Gouty Arthritis and GOUT

An Ancient Disease with Modern Interest

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This book is dedicated to our respective wives,
Catherine and Ann

PREFACE

INCREASING interest in arthritis and rheumatism and availability of newer methods for studying metabolic disturbances have invited more attention to gout and its complications In the past a few perspicacious clinicians made up the sparse observation posts of this interesting, rather common malady Recently, contributions have been more numerous and from a wider orbit. Much remains to be added to our knowledge of this subject, and because of wholesome ebullition by excellent investigators in the field, greater understanding of this clinical puzzle is forthcoming This compilation of theories, facts, clinical observations, pathology, treatment and extensive bibliography was undertaken to furnish the student, clinician and investigator with a usable reference on gout.

The editing of this monograph is credited to Miss Selma DeBakey, Head of the Editorial Department, Alton Ochsner Medical Foundation, the photography to Mr and Mrs George Atkins, Department of Photography, supervision of the material on roentgenographic observations and its discussion to Dr. Seymour Ochsner, Department of Radiology, Ochsner Clinic, and the bibliographic assistance to Mrs. Jean Halliday and Mrs L Zeringer The bone sections were prepared in the Bone Laboratory of the Alton Ochsner Medical Foundation under the direction of Dr Mary Sherman These few furnished so much of the effort that made this monograph possible Any notable contributions are probably theirs, and all errors are the authors'.

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GOUT

Chapter I

INTRODUCTION

General Aspects. Gout is a familial disorder of unknown etiology associated with altered uric acid metabolism and hyperuricemia, occurring predominantly in men and characterized by recurring acute attacks of painful arthritis possibly accompanied by sodium urate tophi. The frequency of attacks of gouty arthritis, the associated diseases, the complications and the treatment required vary.

The term, gout, is derived from the Latin word, "gutta," meaning a drop or coagulation. The implication was that a noxa entered the joint, usually from the head or some internal organ. Delpeuch (84) considered the words, gutta and humor, to be synonyms, and stated that the former replaced the classical Latin expression, for it was a lay term that could be readily understood. He added that by contrast, *between the ninth and twelfth centuries*, use of the word "embarrassed the pens" of the physicians. Guilbert (133) considered "goutte" to be an unscientific name that apparently originated in an uncivilized century. The first record of use of the word is generally accepted to be in the writings of Raoul Bocking (Radolphus Bockingus), published about 1270, concerning a servant of the bishop of Chichester, who cured his "gutto" by wearing the bishop's boots (133).

So protean are the clinical features of gout that the patient may seek initial relief from a general practitioner or a specialist. The orthopedist must differentiate gout from traumatic or infectious articular disease. The sur-

geon may encounter patients with postoperative acute arthritis, which he may mistake for painful phlebitis. The urologist should be aware of the complications of renal disease and lithiasis, associated with hyperuricemia. Even the research chemist and student of basic sciences recognize the gouty patient as a stimulus to the study of purine metabolism The unknown etiology of this disorder remains a constant and stimulating challenge to all those familiar with one of man's oldest and oddest maladies.

History. The first description of gout is generally attributed to Hippocrates in 400 B.C. (1), although the condition was probably recognized earlier (213, 144). In his classical clinical description of gout in 1683 Sydenham (319) did much to differentiate the disease from other articular disorders and opened the way for the modern history of gout

Galen (131 to 200 A.D.) has been credited with the initial description of a tophus. Recognition that gouty tophi are composed of uric acid has been attributed to Wollaston (376) in 1797 Prior to this Scheele (281) identified uric acid as a constituent of a renal stone. It is of historical interest that according to Butt (61) an Egyptian mummy (4800 B C.) was found to have a vesical calculus with a central nucleus of uric acid.

In 1854, by a simple thread test, Garrod (120) demonstrated that patients with gout had hyperuricemia. He showed that if a fine linen thread were placed in a dish containing 2 drams of acidified serum and if, in eighteen to forty-eight hours, the serum uric acid concentration were above 0.025 grams per 1000 grams of serum, uric acid crystals would form on the thread.

In 1871, Miescher (231) described nucleoproteins as the main constituent of cell nuclei, and in 1907, von Fischer (106) elucidated the structure and relationship of uric

acid and many purines Earlier he had noted that salicylates increase excretion of urates In the early 1930's, Folin (108) and Benedict and Behre (25) furnished simple chemical methods for searching for hyperuricemia. Later, improved methods for determination of uric acid based on the specificity of the enzyme, uricase, were introduced Subsequent contributions will be discussed later.

Colchicine was possibly used as a poison before Alexander of Tralles first used it in the treatment of gout in the sixth century A D Strangely enough, in his classic description of gout Sydenham (319) did not mention the drug for treatment of this disease It is not clear whether Baron Van Stoerck, who introduced meadow saffron (colchicum autumnale) to Europeans in 1763, actually ever used the medication specifically for gout (143)

Hartung (144) expressed the opinion that colchicine was first used medically as one of many ingredients in a potent medicine made by an officer in the French Army named Nicolas Husson This preparation was found helpful for acute attacks of gout In 1814, Want (318) learned that the extract of the corm of colchicum autumnale was the ingredient in this patented concoction that was specific for acute gouty arthritis Garrod's publication (121) in 1859 contains a classic description of colchicine With the exception of his lack of knowledge of the effect of colchicine on mitosis, he offered an almost complete picture of its pharmacologic action to which little has been added, even 100 years later.

Classification. Gout may be classified simply into 1) primary gout, or classic or hereditary gout, and 2) secondary gout, or gout usually associated with disturbances of the hematopoietic system The term, gout, implies a general metabolic disturbance with phases of acute and

chronic gouty arthritis, interspersed with intervals of freedom from attacks. Any of these phases can occur in the primary or secondary forms of the disease.

The term gouty arthritis should be used to describe the inflammatory articular changes presumably resulting from the metabolic alteration and deposition of uric acid. *Acute gouty arthritis* is the most common form of gout encountered clinically and implies an acutely painful joint marked by the cardinal signs of inflammation, which usually lasts a short time and responds dramatically to specific therapy. The term, acute gout, has a similar meaning. Rarely, a patient with gout will suffer from continuously recurring acute attacks of gouty arthritis The symptoms merely diminish in intensity but the patient has no periods of freedom from acute articular manifestations of the malady This has been called "polycyclic continuous acute gouty arthritis" (367) and is merely a variant of acute gouty arthritis.

Interval gout may be defined as the asymptomatic intervals between attacks of acute gouty arthritis when no gross residuals are evident but hyperuricemia remains as a reminder of the metabolic disturbance This is also known as the *interval period* or *intercritical period of gout.*

Chronic gouty arthritis implies that stage of gout when residual damage to joints is evident. Urate deposits may be in and about joints and motion of the joints may be restricted Fortunately, this occurs later in the disease and usually after repeated attacks of acute gouty arthritis, with shortening of the asymptomatic intervals.

Asymptomatic hyperuricemia in a person with a family history of gout (or possibly diabetes mellitus) could be considered as *larval gout.* Such a person is predisposed to the development of gouty arthritis.

Gout and hyperuricemia are not interchangeable diagnoses. Hyperuricemia occurs frequently without associated arthritis or gout in patients with toxemias of pregnancy, nephritis, starvation, acute infections, pernicious anemia and blood dyscrasias.

Chapter II

ETIOLOGY

THE etiology of gout is still unknown, although as early as the second century A.D. Galen (156) recognized the hereditary* nature of the disease. In one of the earliest statistical studies on gout Scudamore (268) reported that 59 per cent of 523 patients' parents or grandparents had the disorder Luff's (209) study of 300 patients with gout in 1907 showed a definite family history of the disease in 81.3 per cent, 25 per cent of these were the parents and 18 per cent the grandparents. Reports in the literature indicate a familial tendency in from 10 to 81 per cent of cases (152, 209) Copeman (76) estimated the chances of development of gout in offspring of parents with gout to be about one in twenty

Gout is known to be associated with altered uric acid metabolism and hyperuricemia. It is generally agreed that the incidence of hyperuricemia is greater in the relatives of patients with gout than in others Talbott (320) reported that of 136 non-gouty relatives of twenty-seven gouty patients 25 per cent had hyperuricemia. A similar incidence was reported by Smyth and associates (301). Talbott (326) believed that if a person has hyperuricemia

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* Apparently even Mother Goose suspected a hereditary feature in gout, for it is said (297)

Lazy Tom with Jacket blue
Stole his father's gouty shoe
The worst of harm that Dad can wish him,
Is his gouty shoe may fit him

long enough, he will eventually have gout Smyth (300) suggested this as a possible explanation for the greater incidence of gout in men (who have a higher incidence of hyperuricemia) than in women He also believed that gout occurs in those persons predisposed to hereditary hyperuricemia

Stecher and coauthors (311), who studied 201 members of forty-four gouty families, showed that hyperuricemia is transmitted by single autosomal genes with an estimated penetrance of 84 per cent in the heterozygous male and 12 per cent in the female relatives These investigators found no females with hyperuricemia younger than fifty years. They concluded that in some families hyperuricemia was possibly due to an autosomal recessive and in others an autosomal dominant gene. Of twenty-nine members of three families with a tendency to gout studied by Wilson (362) 72 per cent (21 members) had hyperuricemia and 38 per cent had gout This was interpreted as confirmation that hereditary transmission of the abnormal biochemical trademark, hyperuricemia, is due apparently to a single autosomal dominant gene with high but incomplete penetrance

Hauge and Harvald (145) employed a different method to investigate heredity in gout. Using blood group systems of known genetic pattern, they were unable to identify any relationship between the predisposition to hyperuricemia and the inheritance of blood groups. Their study of 261 relatives of thirty-two male patients with gout suggested a cumulative genetic influence, which is not unusual for inheritance of normal characteristics.

Two additional views regarding the hereditary tendency to gout have only traditional sanction One is that maternal predisposition seems to carry a greater risk to

the offspring than paternal predisposition. The other is that the older members of a gouty family do not suffer as much as the younger.

Some have tried to correlate the incidence of gout with the patient's economic status, his indulgence in alcoholic beverages, and his qualitative dietary habits, but there is no real evidence to substantiate this. In fact, the cartoonist's classical depiction of the person with gout as obese, jovial, and addicted to red wine, rich food and high living is only partially true. The typical American patient with gout whom we see is about 15 to 20 per cent overweight. About 45 per cent of the patients with gout whom we have questioned regarding their diet consumed a small or normal amount of meat, an equal number favored a high meat diet, and only 10 per cent had a high purine diet. Seventy-two per cent of our patients were drinkers of alcoholic beverages, wine was used least by these, beer more commonly and heavy distilled spirits most. Eighteen per cent of our patients were non-drinkers. In our series white collar workers outnumbered laborers and professional men five to one.

Racial and Geographic Incidence. There seems to be no racial preference in gout. The disease has been found among the Asiatic Indians, Chinese, Italians, Indians of South Africa, Jews of all nationalities, Germans, English, Scandinavians, Russians, French, Irish and Filipinos (105, 212, 322) We are not aware of extensive reports of gout in Latin America, but of 265 patients with proved gout seen at the Ochsner Clinic twenty-two were Latin Americans Although gout has been found in patients practically the world over, its incidence varies from country to country even when this includes a small geographic area It has been pointed out that whereas the condition is almost nonexistent in Finland and is seen infrequently

in northern Sweden, it is common in southern Sweden and Denmark (46).

Color. According to Talbott (327), the American Negro is highly immune to gout. Until 1953, there were reports in the literature of only nine cases of gout in the Negro (71, 361). This probably does not give the true picture For example, at the Cook County Hospital in Chicago, Illinois, the relative incidence of gout was 0.06 to 0.10 per cent for Negroes and 0 04 and 0 20 per cent for white patients (237). During a period of thirty-six months a diagnosis of gout was made in seven Negro patients at the Tulane Arthritis Clinic in New Orleans. The clinical picture of gout in these Negro patients was atypical in that there was a greater tendency to chronicity of articular symptoms and the gouty arthritis was more resistant to conventional therapy One of us (T E W) has seen one Negress with gout Perlman and associates (254) reported one case and Rodnan and Colomb (273) reported six cases However, an American physician, practicing in Nigeria, has seen no natives with gout (123)

Sex. Gout is a disease predominantly of men The reported incidence in men in large medical centers is about 95 per cent, or a ratio of nineteen to one (76). Smyth (299) pointed out that hyperuricemia is not demonstrable until after puberty and that gout has not developed in men whose gonads have been removed Gout is not common in women but tophaceous gout has been reported in females (69, 330) Tophaceous gout in females usually occurs before the menopause, and when present, probably is a severer type than ordinarily occurs in this sex Of the thirteen female patients with gout that we have observed seven had undergone the menopause more than ten years before, four less than ten years before and only two had not yet reached the menopause The

clinical picture of gout in females is more varied and there is a greater tendency towards involvement of multiple joints (338) Rosenberg (275) reported a case of gout in a person with bisexual genitals, whose personality was predominantly feminine, but whose body configuration was masculine; excretion of androgen was high.

The average plasma urate level in normal men is higher than that in normal women but the reason for this is not known It has been suggested that possibly this difference is due to greater urate clearance, altered urate biosynthesis and lesser muscle bulk in the female (135, 137). Talbott (324) noted a low fertility rate in married women with gout and he has not observed a woman with well developed tophaceous gout who had children The problem of fertility in men with gout is probably not comparable with that in women. Only 21 per cent of the men with gout whom we have seen were not fathers.

Age. Since there is a hereditary tendency in gout, the metabolic defect is probably present at birth. The initial attack of acute gouty arthritis usually occurs in the fourth or fifth decade of life, although it may occur early in the first decade or as late as the tenth decade. Acute gout is not unduly rare in patients older than seventy years. Schopf (284) reported a case of gout in an infant five weeks old with urate deposits in the kidneys and about the carpal areas of the hands, in that short span of life the dorsum of the hands had become thickened and puffed The infant failed to gain weight and gastrointestinal symptoms and pneumonia developed. Another case of gout was reported in a girl twenty-three years old who had been troubled with articular symptoms since the age of three and one-half years (265). Attacks of gout that occur in the first decade of life are usually incorrectly diagnosed, and occasionally they are associated with the

blood dyscrasias that are common in children (344) One of us (T.E.W.) saw a patient who had had acute gouty arthritis from the age of seven years until the age of twenty-six years, when urinary symptoms led to the suspicion of gout Berk (30) reported destructive gout in a twenty-nine-year-old man which had been present since the age of eleven years

Hyperuricemia, which usually precedes the arthritis, may occur at any age but it is unusual before puberty. The earlier in life the attacks of gouty arthritis occur, the more likelihood there is of increasing severe disease, with crippling articular damage.

Chapter III

PHYSIOLOGY

It is generally agreed that the metabolic defect in gout is characteristically expressed as elevated concentration of uric acid in the plasma. Although there is no obligatory correlation between the presence of elevated serum uric acid and the clinical entity of gout, some believe that gout will eventually develop in patients with hyperuricemia.

Man, the other primates and the Dalmatian coach dog occupy a unique position among mammals, since they all excrete significant amounts of uric acid. In other mammals uric acid is converted to allantoin for excretion. Buzard and coworkers (63), using isotopically labeled uric acid in a normal man and in a patient with gout, observed that in neither were significant amounts of the labeled uric acid converted to allantoin.

Hoffman (156) made an interesting comment in this regard. He stated that all primates really have the inborn error, but that in those with hyperuricemia this is probably exaggerated In essence, man has two factors that favor an elevated serum uric acid level: absence of uricase in the liver for conversion of uric acid to allantoin and renal tubular resorption of uric acid. The levels of uric acid thus found, even in normal people, are dangerously close to the saturation level. The Dalmatian coach dog achieves hyperuricosuria by not resorbing uric acid in his renal tubules.

The mammal may obtain uric acid in three different

ways: 1) ingested food or injected substances; 2) breakdown of all types of body cells, and 3) products of biosynthesis within the body.

Cells contain nucleic acid of two types. One is ribose nucleic acid (RNA), which is in the cytoplasm, and desoxyribose nucleic acid (DNA), which is in the nucleus RNA is continuously broken down and reformed, whereas DNA is more static and is apparently related to the genes

Formation of uric acid in the body depends on availability of precursors, direct transformation (oxidation) of the formed purines, speed of cellular development and rate of formation of purines from the precursors Uric acid is one of the end products of nitrogen metabolism in man Although the major normal source of uric acid in man is thought to be the metabolites of nucleic acids of the body, glycine, when ingested, can rapidly be incorporated into the uric acid that is then found in the urine There is evidence that glycine furnishes both the nitrogen and carbon atoms for formation of uric acid (169, 294) Bishop and coworkers (38) believed that glycine is incorporated into some other uric acid precursor before being used for production of uric acid In some patients with gout labeled ingested glycine appears to be converted to urinary uric acid at a greater rate than in those without gout (27), whereas in other patients with gout this does not occur (28, 236) These observations are difficult to reconcile with the greater volume of distribution of uric acid and lesser turnover rate in patients with gout Even with greater production it would be hard to explain unless uric acid synthesis from glycine takes place in the kidney About 25 per cent of people with gout have hyperuricosuria, and if this can be related to the rapid conversion of a precursor, such as glycine, it would be likely that

over-production of uric acid does exist in some patients with gout.

α-tocopherol might be important in the metabolism of glycine to uric acid. In one study, intensive, long-term vitamin E therapy in a non-tophaceous patient with gout resulted in conversion of the rate of metabolism of glycine to uric acid to normal (38). It was believed that a major difference between the gouty and normal person may be a more rapid turnover of a precursor of uric acid to uric acid exemplified by these glycine studies and that this may actually be due to a defect in vitamin E absorption or metabolism. One objection to this, of course, is that vitamin E deficiency is almost invariably associated with pronounced creatinuria, which is absent in patients with gout.

Spilman (309) noted that C^{14} administered as formate appeared more rapidly and in greater concentration in the urinary uric acid of patients with gout than in normal persons. It was proposed that hyperuricemia in such patients is due to greater formation of urate by non-*nucleoprotein routes*

The citrovorum factor (CF) may be a closely related compound in formation of purine and uric acid, and alteration of metabolism of this compound has been considered as a possible defect in the patient with gout. Limited studies suggest that *CF as well as folic acid (FA) may* act as "transformylating agents" in formation of purine. Studies of the conversion of pteroylglutamic acid (PA) to CF have been reported as showing that after oral administration of FA or intramuscular administration of CF the average urinary CF in patients with gout was significantly less than in normal persons; this suggests that either increased CF utilization or renal retention of CF is present in the patient with gout (98).

It has been demonstrated in animals that the tissue xanthine oxidase, which catalyzes oxidation of xanthine and hypoxanthine to uric acid, is elevated when a folic acid deficiency exists (168, 360). A patient with nontropical sprue and hyperuricemia was reported to have been treated with folic acid with correction of the anemia and decrease of the hyperuricemia, this suggests clinical demonstration of the possibility that the increased serum uric acid is associated with a folic acid deficiency (393). Bishop and coworkers (38) in their studies with glycine as a precursor, and later Zumoff (394) in his studies, were unable to show any effect of administration of folic acid on uric acid metabolism

Lewis and co-authors (197), who studied the effect of amino acids on excretion of uric acid, noted that glycine and alanine produced a sharp increase in urinary uric acid whereas ammonium chloride and urea had no effect. Although this observation has been confirmed in studies using isotopically labeled glycine, we are not aware of any comparable studies using alanine Studies in which isotopically labeled material was used demonstrated, usually in the pigeon, that carbon dioxide, formate, lactate, serine, glycine and threonine are incorporated into uric acid (39, 55, 94, 146, 305) Precursors of the labeled atoms in the uric acid ring were outlined by Bauer and Singh (23) as follows C_4 C_5 N_7 are derived from glycine, N_1 N_3 N_9 are derived from ammonia, C_2 C_8 are derived from formate, C_6 is derived from carbon dioxide (Fig 1)

It has been said that the glutamine and oxypurines of plasma are related to the hyperuricemia and that the glutamine content, which is a precursor of uric acid, is low in patients with gout whereas the oxypurine content is high (245) Various authors, especially Segal and Wyngaarden (290), were unable to confirm this obser-

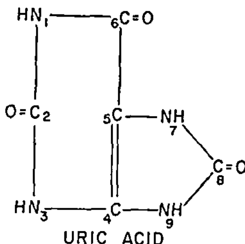


Fig 1. Precursors of labeled atoms in the uric acid ring (from Bauer and Singh (23)).

vation. Weissmann and coauthors (358) showed that in acute gouty arthritis excretion of 8-hydroxy-7-methyl-guanine *is increased and that in interval gout excretion* of hypoxanthine and xanthine is decreased

Wyngaarden (381) also reported that gouty subjects fed glycine-1-C^{14} have urinary excretion curves resembling those reported by Benedict and associates (27), who fed N^{15} labeled glycine They believed this to be consistent in gout regardless of the stage of the disease, but this was not the experience of Seegmiller and coworkers (288). This corresponds with the view of Benedict and associates (28) *that in some patients with gout such curves foster* the view of a "shunt mechanism" for urate synthesis from dietary glycine without obligatory intervention of nucleic acid purines It has been possible to inhibit incorporation of glycine into uric acid in normal subjects by concomitant administration of 4-amino-5-imidazolecarboxamide-4-C^{13} (289).

In general, the elevated value for any organic constitutent that can be synthesized in the body can be due to more rapid absorption, over-production, reduced metabolism, diminished excretion or a combination of these. It has been possible to synthesize both uric acid and some of its precursors containing isotopically labeled nitrogen, carbon or both. These labeled compounds can then be administered to normal and gouty subjects and the distribution in their body fluids measured

With the advent of methods in which isotopes of nitrogen (N^{15}) and carbon (C^{14}) are used, it was hoped that a solution to the defect in uric acid metabolism manifest in patients with gout could be easily found Unfortunately, this has not been the case It has been possible to evaluate uric acid excretion and turnover rates of uric acid in the body (315), and patients with gout appear to have larger miscible pools of uric acid, and their turnover of the uric acid pool is slower than that of normal persons

The normal miscible pool of uric acid varies from 700 to 1600 mg. (average slightly more than 1000 mg.) whereas in patients with gout it ranges from 2000 to 31,000 mg The daily turnover rate for normal persons is from 0 50 to 0 90 pools whereas for the patient with gout it is only 0 35 to 0 50 pools

Although a miscible pool of uric acid may be ten to fifteen times greater in one patient with gout than in another, the serum uric acid levels may not be remarkably different This underscores the fact that a simple serum uric acid determination fails to give a true picture of the amount of uric acid in the body. In general, it would appear that the average excretion of injected uric acid in the urine is less in patients with gout than in normal persons However, Gutman and Yu (138) observed that 25

per cent of 100 patients with gout excreted more uric acid than the normal maximum

Little has been added to this by the use of isotopic uric acid since this observation was made in the classical studies of Folin and coworkers (109) in 1924. The additional observation by Buzard and associates (63) was that not only is the isotope excreted more slowly but it is apparently impossible to account for the entire label injected as readily in patients with gout as in normal persons. Although they do not mention it, it is possible that this extra uric acid is deposited in the tissues. We relate it to the fact that the pool size in patients with gout is actually larger and therefore one would expect a smaller percentage of the injected material to be excreted in a given period of time. There seems to be general agreement that when such a procedure is carried out, the uric acid is distributed through a larger volume in the patient with gout than in the normal subject. This means, in metabolic terms, that there is a larger miscible pool in which the labeled uric acid is distributed

If then, in addition, excretion of the labeled uric acid is studied, a value is obtained for the turnover rate in terms of the total pool Here again, there seems to be agreement that normal subjects have a greater turnover rate (in terms of pools/day), namely, from one-half to nine-tenths of the uric acid pool is turned over each day, whereas from one-third to one-half of the metabolic pool of uric acid was turned over in the patients with gout studied This is even more impressive when it is realized that the tophi probably only exchange with the labeled uric acid on their surface so that in addition to the miscible pool, the patient with gout undoubtedly has a large additional non-miscible store of uric acid, or more properly, sodium urate.

The physicochemical state of the uric acid in the body fluids in its relation to the size of the miscible pool, and to deposition of uric acid in tophi, has been the subject of many experimental investigations and much speculation. It is interesting that the solubility of sodium urate in distilled water is considerably higher than that of sodium urate in either serum or plasma. Also, more sodium urate will dissolve if one waits a long time than if one waits only a short time. Nonetheless, as far as we know, no one has ever seen a solution of sodium urate in body fluids that approaches the solubility in distilled water. This uric acid is not diffused into the red cells because the concentration in serum is apparently invariably greater than that in red cells (39).

The concept of protein binding of uric acid, which was reviewed extensively by Bishop and Talbott (39), is attractive. Adlersberg's (3) observations that the nonfilterable (presumably protein-bound) fraction of serum uric acid varies with the activity of the gout supported this concept. Bene and Kersley (24) were unable to confirm Adlersberg's observations, and this was also our experience. However, since this might have been due to faulty technic, an alteration in method was sought.

Ultracentrifugation of serum serves to stratify the serum protein, and this was taken into account. Sera from 15 patients with gout were ultracentrifuged and the top and bottom layers were separately analyzed for uric acid. All specimens contained a greater concentration of uric acid in the bottom half of the tubes (Fig. 2). In all four patients with tophaceous gout the difference between the two layers was striking (2.0 to 5.2 mg. per cent). Of eleven patients without gouty tophi only two had overlapping values (2.4 and 4.2 mg. per cent). In the remaining nine lesser differences were noted (0.2 to 1.4 mg.

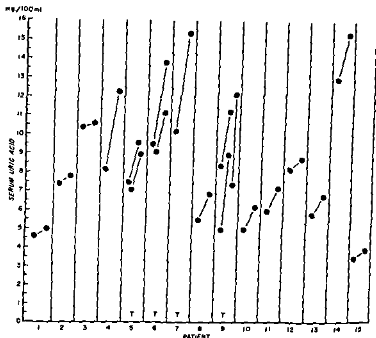


Fig 2 Values for serum uric acid determinations on specimens that were separated into two parts by use of the ultracentrifuge In each case the lesser quantity of serum uric acid was in the top half of the tube centrifuged and the greater amount was in the bottom half of the tube This difference in the serum uric acid values of the top and bottom halves of the tube was not great in 9 of 11 patients with gout. In all patients with tophi (T) a significant difference in the serum uric acid levels was noted in the top and bottom specimens examined.

per cent) These preliminary data would suggest a difference in the physical state of the serum uric acid in tophaceous gout. Thus, we postulate that deposition of uric acid as tophi is fostered by ingestion of the uric acid-protein complex by the urophages associated with the granulomatous reaction seen in tophi Studies by others

(279, 343) of the electromigration on filter paper of serum uric acid failed to indicate any particular chemical form of uric acid or a binding with other serum components

The problem of uric acid excretion in the bile, subsequent excretion in the stool and possible reabsorption from the gastrointestinal tract with enterohepatic circulation is interesting There seems to be no question that bile either before or after death contains more uric acid than the circulating blood Minibeck (233) reported that the duodenal mucosa actually secretes uric acid, and Schroeder and Raginsky (285) thought that the degree of excretion throughout the entire intestine paralleled blood uric acid levels Paroulek (250) concluded that exogenous uric acid is completely removed from the circulation by the liver At present it is difficult to decide whether the enterohepatic circulation contributes a large part to the metabolism of uric acid, although it would appear that intestinal flora may actually destroy uric acid in this fashion Indeed, it has been suggested that the intestinal flora of patients with gout may be different from that of normal people If hyperuricemia is due to the possible inability of the intestinal flora to destroy uric acid coupled with ability for synthesis, then what one "inherits" is a characteristic gastrointestinal flora! However, it has been shown that intestinal bacteriostasis does not decrease uricolysis (383).

Although theoretically the enlarged pool size and the elevated serum uric acid are due to decreased destruction or decreased rate of urinary excretion of uric acid, cases have been reported of patients with gout studied both with and without isotopically labeled uric acid, who excreted excessive amounts of uric acid in the urine

The role of the kidney in gout continues to be of interest. Thannhauser's (336) theory attributing the

hyperuricemia of gout to excessive tubular resorption of urates in the kidney is attractive. Stetten and coauthors (316) believed that it lacks adequate experimental or clinical verification

Some observers (31, 116), believe that urate excretion is not impaired in patients whose renal function is normal On the other hand, others (343) noted increased tubular resorption of uric acid and reduced urate clearance in patients with gout Failure to concentrate urinary urates in the presence of an increased miscible pool of uric acid does not preclude the presence of impaired excretion of urates

Impairment of renal function is considered the result, not the cause, of the metabolic defect of gout. Indeed, it would appear that although the excretory rate of uric acid of patients with gout is low enough so that the serum uric acid level is not lowered and the size of tophi is not decreased, it nevertheless is high enough so that uric acid can precipitate out in the kidney itself, or in the form of uric acid renal stones. In such patients advanced renal damage may develop from precipitation of uric acid With further reference to the fact that it is probably not uniformly the case that there is excessive uric acid in the urine, polycythemia vera, myeloid metaplasia and the leukemias also lead to excessive excretion of uric acid in the urine, associated with high serum uric acid content It has been reported that an increase of 1,000,000 red blood cells results in an increase of 10 grams in the endogenous uric acid (270). In these conditions it is not unusual for a high circulating urate level to be associated with deposition of sodium urate crystals in the joints and acute articular symptoms which may actually respond favorably to administration of colchicine. It has long been our belief that the relationship between polycythemia vera and gout is more than fortuitous. Myelogenous leu-

kemia, another condition associated with high serum and urinary uric acid levels, later develops in many patients who have polycythemia vera. An attractive hypothesis is that these essentially neoplastic diseases have a greatly excessive rate of nucleic acid synthesis and degradation and thereby mimic the hyperproduction of uric acid in primary gout, and the other events follow as a natural consequence.

Uricolysis with cytochrome-cytochrome oxidase (132, 220) leucoperoxidase and verdoperoxidase has been observed (61, 383). Similar oxidation has been reported when uric acid was incubated with human erythrocytes and leukocytes (34). Pollycove and coworkers (258) studied uricolysis in the human, using uric-2-C^{14} acid and measuring the excretion of $C^{14}O_2$. They reported that in subjects with hyperuricemia more body uric acid is oxidized to CO_2 than in normal people. All of this is supporting evidence that uricolysis does occur and must be taken into consideration in the pathologic physiology of gout. Early studies on one patient who was given uricase injections for three days failed to show any change in the uric acid level (243). More recently, it was reported that injection of purified uricase into the human does elicit a uricolytic effect (205).

It is of interest to note that in hairy animals the hair has been found to have a high uric acid content, and that likewise all keratinous appendages including quills, horns, hoofs, nails and claws have a uric acid content that is greater than the animal's blood level. It is possible that molting and dousing feathers are means for getting rid of uric acid (43).

Colchicine is one of the most effective drugs in gout despite the fact that it has no demonstrable effect on the levels of uric acid in the blood or urine. There are several

agents that increase the uricosuria. One of these, pro benecid, has often been successful in increasing uric aci excretion to the point that the serum uric acid level reduced and the recurring acute symptoms are relieved Aspirin and other salicylates also have readily demon strable uricosuric properties. Yu (385) raised the poss bility that tubular excretion of urates may exist and possibly affected by salicylates and probenecid. Afte administration of probenecid and aspirin the uricosuri is not additive, indeed, when the two drugs are given to gether, less uric acid is excreted than when either is give alone Salicylates have been found also to counteract th uricosuria of zoxazolamine, which is a potent uricosuri drug (60). ACTH and cortisone are also uricosuric agent and can be employed in the treatment of the acute attack However, their extended administration does not decrease the circulating uric acid level.

In the antithesis of gout, Wilson's disease or hepato lenticular degeneration, the urinary uric acid level i elevated and the serum levels are low. Like the Dalmatian coach hound, these patients seem to have a defect in the renal tubular resorption of uric acid.

As far as the metabolism of uric acid and its expression in acute gout is concerned, there appears to be a typical form of hereditary gout associated with over-production of uric acid, an increased pool size and a decreased rate of pool turnover. There are no other consistent findings and at present this appears to be a real error of over-production of uric acid However, there are probably other instances of increased production, decreased de-struction, and decreased excretory rates in various com-binations that may also lead to clinical hyperuricemia and to the acute articular manifestations known as gout. Unfortunately, to date, no common denominator has been

found except the elevated serum uric acid and the increased miscible pool size that would enable us to analyze the uric acid defect further in patients with clinical gout

Because gout is rarely encountered in children, premenopausal women and eunuchs, and has a predilection for men, the role of the endocrine glands has been considered in the physiology of gout It was once suggested that androgenic activity played a role in the pathogenesis of gout (372) and that an abnormal adrenocortical androgen determined development of the hyperuricemia and appearance of the clinical manifestations of gout (366) These suggestions were in part based on the observations that in patients with gout the urinary 17-ketosteroid excretion was reduced, as well as that early in the acute attack of gout the amount of serum cholesterol may be reduced (73, 201). It was supposed that the serum cholesterol was utilized for the synthesis of adrenocortical hormones, which, when metabolized, do not result in 17-ketosteroid excretion (371) As has been our experience, Butt and Marson (62) noted that the 17-ketosteroid excretion of thirty-three patients with gout was in the normal range

Final interpretation of the 17-ketosteroid excretion remains to be found Robinson and coworkers (272) stated that there is at least suggestive evidence that patients with gout excrete a smaller proportion of adrenocortical steroid as 17-ketosteroids than do normal persons They thought that it was no longer necessary "to postulate the existence of the hypothetic 'gouty androgen' referred to in their *Tenth Rheumatism Review* in order to explain these observations"

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not thought to be statistically significant and was not observed in older patients Other studies have failed to substantiate evidence of increased adrenocortical activity in patients with acute gout, and the response of such patients to administration of ACTH was considered normal (194).

Wolfson (366) also amplified other supposed functions of adrenocortical activity and acute gouty arthritis which had been suggested earlier (147, 331). He maintained that the acute attacks of gout brought on by ACTH withdrawal or stress (postoperative) may be associated with a delay in the rebound to physiologic levels of the 11-oxysteroid activity, and presumably in the gouty patient *indicates an abnormality in the release of endogenous* ACTH, either by dysfunction of the pituitary gland itself or the hypothalamic neurohormonal mechanism described by Hume (162) Levin and associates (194) speculated that an attack of acute gouty arthritis may not stimulate the pituitary adrenal axis or that an unknown regulatory mechanism may be active which could account for the metabolic changes in patients with gout after stress of withdrawal of ACTH These observations are probably best interpreted as changes occurring in the metabolic interplay of gout rather than its etiology Robinson and associates (271) failed to demonstrate any evidence of a rebound in hormonal activity during the post-injection period.

Although attempts have been made to attribute the acute symptoms of gouty arthritis to allergic reactions to food, pollen or infection, there is little evidence to support this contention (142, 240). We have had only one patient with gout who has been satisfied with the use of an antihistamine to relieve hi 'outy arthritis Hench

(150) believed that skin tests and elimination diets have no place in the management of gout.

The pathologic physiology of acute gouty arthritis is not understood Intravenous infusion of uric acid into men who do not have gout, which resulted in a serum uric acid level up to 26 mg per 100 ml, has failed to cause gouty arthritis (31). The same negative results have been noted in patients with gout given intravenous infusions of uric acid (about 20 mg. per kilogram) (109) Oral ingestion of uric acid or its subcutaneous injection about joints also failed to cause acute gout.

The precursors of uric acid have also been tested in the same manner, and although adenosine and its phosphorylated derivatives have a wide variety of systemic and some local inflammatory effects (79), these reactions do not appear to simulate acute gouty arthritis. Thannhauser and Bommes (337) produced acute arthritis with adenosine but this could not be reproduced by Gutman and Yu (137)

During the acute attack of gout the urinary excretion of 8-hydroxy-7-methylguanine may be increased Although this may not be a specific metabolic abnormality for acute gout and occurs in other conditions of excessive turnover of nucleic acids, it is the first alteration of purine metabolism demonstrated during the acute stage of gout (390)

Current observations are not in keeping with many of the older opinions that acute gouty arthritis is precipitated by deposits of urates in the peri-articular region or rupture of such deposits into the articular space (47, 92) It has also been the contention that minor trauma to the site may initiate urate deposition, with subsequent attacks adding more urates There is no convincing evidence that tissue must be damaged in order to precipitate formation

ırates Local trauma could cause a greater localized ıd flow which may add to this localized deposıtion of ːes There ıs additıonal evidence that in acute gout blood flow ın the ınvolved sıte is increased consider-, and that at these times there may be some derange-ıt of the artenal venous peri-articular plexus whıch ld account for the phenomena of the acute attack and tophı (167, 370).

Chapter IV

PATHOLOGY

Gout is characterized by elevated uric acid content of body fluids and sometimes, in addition, by deposition of sodium urate in the tissues and joints It is these deposits that lead to the pathologic alterations characteristic of gout The relationship between the elevated uric acid levels in body fluids and deposition in the tissues is not clear, since the latter effect is not an obligatory accompaniment of hyperuricemia

The granuloma or tophus is pathognomonic of gout It has many similar microscopic features whether it is found in the skin, kidneys, bursae, other soft tissues or osseous structures (276). Histologically, this lesion usually comprises the peripheral zone of fibrous supporting tissue, blending with the normal cellular component of the structure in which it lies This peripheral zone surrounds an intermediate area of increased cellularity or inflammation similar to the histologic picture of a true tubercle The composition of the tophus varies, but usually lymphocytes, plasma cells and large multinuclear reticulo-endothelial cells are to be found in the typical lesion The giant reticulo-endothelial cells that contain urate crystals have been referred to as urophages Within this ring of inflammatory changes are deposits of crystalline bundles of urates separated by an amorphous matrix (Fig 3-7)

The composition and nature of the matrix has not been clearly defined It has sometimes been found to contain







Fig 7. Section of toe Uric acid tophus in bone (Low amphyplan, 10 X objective, 27 cm)

Fig. 8: Metatarsophalangeal joint in a patient with gout of ten years' duration. Note the urate crystal "frosting" on head of phalanx

lipids, including cholesterol (68) and polysaccharides. With the aid of special stains, the matrix in some areas is metachromatic or has shown a reaction suggesting the presence of mucoid substance, and in some nodules, has been found to include a small quantity of reticulum (301) Cell debris is not common, and when present, is associated with local trauma and possibly interference with the local vascularity. Demonstration of urate crystals is essential in order to label these granulomas accurately as gouty lesions, for small rheumatoid arthritic nodules may closely resemble the granulomatous tophus. The urate crystals may not be identifiable if the tissue is improperly fixed and stained Deposits of urate crystals may be found in soft tissues or bones devoid of associated inflammatory changes.

Kidneys. The kidney is a common anatomic site of pathologic alterations in patients with gout The characteristic alteration is deposition of sodium urate and uric acid, primarily in the renal medulla, though it may be found anywhere in the kidney or its excretory ducts There may be no granulomatous reaction Since the opportunities for examining the kidneys of patients with early gout are few, the exact pathogenesis is not known However, the medullary and extrarenal urate collections in essence produce blockage of the renal excretory system with resultant chronic pyelonephritis in a high percentage of cases Most kidneys removed because of uric acid stones contain pathologic changes compatible with chronic, subacute and acute pyelonephritis The term "gout kidney" or "gouty nephritis" has not been sharply defined, and as suggested by Lichtenstein and coworkers (198), it seems more appropriate to restrict such reference to kidneys containing appreciable deposits of urates in the renal parenchyma Generally, varying degrees of

arteriosclerosis, chronic pyelonephritis, urate deposits and interstitial fibrosis are observed in the affected kidney of patients with severe gout

The gross changes may be minimal. The usual picture is that of an atrophic kidney with a pitted granular surface from which the capsule is stripped with difficulty. Some patients with gout have grossly normal kidneys. All gradations between the two extremes are possible. The cut surface may show definite cortical and medullary delineation, or these may be indistinguishable. When the kidney is cut, a gritty sensation may be the first intimation of uric acid deposits Grossly, chalky, yellow-white deposits may be present in the medulla and they may radiate as small streaks throughout the renal substance. The pelvis and calyces may be dilated, and the ureteral walls may be thickened. Dirty grey or mustard-colored stones or uric acid sludge may be present in the pelvis of the kidney.

Microscopically, the urate deposits are associated with the collecting tubules. Brown and Mallory (50) believed that these urates are deposited initially in the tubules. Localized foreign-body reaction probably aids in destruction of the tubules. Some tubules may be dilated and glomeruli may be obliterated. Modern and Meister (234) suggested that the collecting tubules are compressed by the urate deposits in the renal medulla and this eventually results in an ascending intrinsic renal lesion with death of the nephron. This is considered the reason for the infrequency of albuminuria in patients with renal damage due to gout. Modern and Meister associated such findings with what they believe is a specific renal lesion of gout characterized by renal insufficiency, fixed urinary specific gravity, azotemia, absence of hypertension, and lack of proteinuria and formed elements in the urinary

sediment of patients with severe renal damage. Schnitker and Richter (283) believed that albuminuria is not commonly associated with gout unless nephritis is present, and they attributed this to predominance of vascular nephritis. Brown and Mallory noted small scattered areas of pyelonephritis or abscesses in two patients with gout whom they studied, and these areas were adjacent to or surrounding deposits of urates The arteriosclerotic change, which seems to occur early in gout, manifests itself in the kidney as nephrosclerosis Small arterial branches have moderately thickened walls and narrow lumens

How or in what order the varied pathologic changes occur in the kidneys of patients with gout is not known. It is logical to conclude that slight changes must occur and that they are not recognized or associated with gout, as the diagnosis of gout is usually a clinical one and the pathologic findings are non-specific

Urate deposits are sometimes seen in the medullary pyramids of kidneys of newborns or infants in the first few weeks of life (8). This has been referred to erroneously as "uric acid infarcts" They represent collections of urates in the collecting tubules devoid of surrounding inflammatory reactions These lesions have no relation to gout, and renal dysfunction has not been attributed to them (5)

Bone. Damage from urate deposits on the articular surface (Fig. 8) occurs frequently but occasionally a joint that has been subjected to repeated attacks of acute gouty arthritis fails to show any discernible pathologic change (Fig 9) Early in gout, articular changes may be minimal and limited to minute deposits of urate crystals on the surface of the cartilage Because the avascular areas in the outer layers of the cartilage are frequently the site of





Fig. 9 Section through second left toe of a man 66 years old with hyperuricemia for 25 years and gouty arthritis for 10 years (serum uric acid 6.1 mg per 100 ml). Note draining tophus on dorsum of distal phalanx The interphalangeal joint is intact despite almost complete replacement of the distal bone with uric acid

Fig. 10 Gross section of the toe showing urate granulomas on the articular surface.

initial urate deposits, it has been suggested that the urates are probably related to the synovial fluid rather than adjoining capillaries. In a description of the pathologic changes in the knee joint of the classical case of gout Lichtenstein and associates (198) noted that the urate deposits were prominent around the edges of the articular surfaces but were sparse at the points of contact Duckworth (92) described urate crystals that projected into the matrix of the cartilage perpendicular to the articular surface

The reason for the initial deposition of uric acid crystals in the cartilage is not known. Possibly, trauma or mechanical breakdown of a small area of cartilage can initiate localized crystallization of urates This is a microscopic reaction and the crystals are deposited radially As urates can be precipitated rather easily, the accumulation grows and a gross urate mass is formed, the cartilage then becomes eroded and thin, and urates are deposited in subchondral bone and synovial membrane (Fig 10, 11) eventually replacing the entire normal structure

Uric acid granulomatous changes are not seen in cartilage but rather in the synovial membrane and surrounding soft tissue A fibrous tissue reaction may also occur in the synovial tissue This can be mild or of such degree that a pannus is formed, which, in turn, is destructive and may cause some of the "bubble-like" areas demonstrated roentgenographically (Fig 12) The fibrous mass can occupy the entire articular space and eventually cause ankylosis similar to that seen in rheumatoid arthritis Osteophytes and degenerative changes form at the edge of the involved joint and this combined with changes due to urate deposits provides the typical picture The changes seen in an involved joint of a classical case of gout will include the presence of chalky white urates in the articular

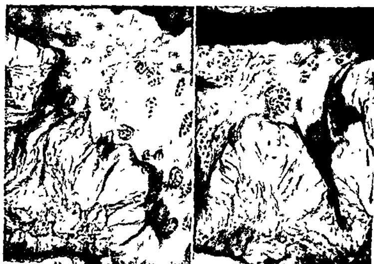


Fig 11A, B Joint surface of the specimen in Figure 10, showing uric acid deposits without granulomatous reaction.

surfaces, variable degrees of destruction of the articular cartilage, thickening and possibly villous formation of the articular membrane Uric acid deposition with granulomatous reactions may occur at sites in bones that are removed from the joints (Fig 9). These lesions enlarge and replace normal-appearing bone without necessarily involving the joint to any significant degree. In such bones are seen variously sized collections of urates and matrix that are ringed by an inflammatory cellular reaction including both foreign body giant cells and macrophages The zone of cellularity is surrounded by connective tissue containing fibroblasts, reticular cells and small mononuclear cells (Fig. 7) Development of new bone has been described in the osseous lesion of a patient with classical gout (198) Calcium deposits may be found within the urate bundles Calcification of widespread



Fig 12 Medullary tophi in base of middle phalanx of ring finger Marginal erosions of proximal interphalangeal joint are associated Note absence of osteoporosis

urate tophi is not common, although a large tophus of many years' duration may contain calcium (Fig 14) Specimens of joint and bone require careful dissection and examination by the pathologist, for small gouty lesions may be overlooked (Fig 13).

Cardiovascular System. Specific pathologic changes related to tophaceous gout have not been found with



ig 13A. Femoral head of a patient whose clinical picture was uggestive of tuberculous arthritis of the hip. Histologic study failed reveal tuberculous lesions, but a small gouty granuloma was found

Area outlined in femoral head Uric acid tophus with granu-atous changes in femoral head (Low amphyplan ocular, 10 X objective, 40 7 cm)



Fig 14 Gout of metatarsophalangeal joint of great toe Soft tissue tophus contains extensive calcification

any frequency in the heart or blood vessels (198). Isolated observations, though, have been recorded In one case a large tophus was the cause for complete heart block (153) In another case a urate deposit was found on a posterior mitral valve leaflet (56) In still another report there was a tophaceous deposit in the mitral valve leaflet that extended over the endocardium (340) Arteriosclerosis is common in patients with advanced gout

Other Organs. Other internal organs that have been studied by pathologists interested in gout have been found to be free of any specific changes that could be associated with this metabolic malady Tophi have been found in the cornea, meninges, bronchi, pleura and tongue but these are undoubtedly medical oddities (299)

TOPHI

Tophaceous deposits of urates are pathognomic of gout. When of significant size or multiple, they usually denote a well-developed stage of chronic gouty arthritis. In rare instances, they have been observed in patients before the initial attack of acute gouty arthritis occurred Tophi are found in less than 2 per cent of patients experiencing their initial acute attack of gout (201)

The helix or antehelix of the ear is the usual site of the initial tophus (Fig 15-17). Urate deposits have been found in the sacroiliac joints (21), sclerae, cardiac musculature (153) and valves (56), and cervical vertebrae (173) (Fig 48), as well as over the extensor surfaces of the fingers (Fig 20a-c), elbows (Fig 19), knees, ankles, toes, heels (Fig 18a, b) and other usual sites In some patients with chronic gouty arthritis, uric acid tophi progressively form about joints in adjacent soft tissue, bursa and bone, which become much greater than similar deposits in the ears.

Tophi are seen in from 13 to 60 per cent of patients with gout (158). In our series of 280 patients 20 per cent had tophi Kuzell and associates (187) reported visible tophi in 13 per cent of the male and 3 8 per cent of the female patients among 520 patients with gout. Sixty per cent of their patients who had had gout ten or more years had visible tophi. Bartels (15) reported a 20 per cent incidence of tophi after eight to ten years of gout. This, though, does not imply that age alone or the duration of the gouty process is directly related to the extent of the tophi In some patients gouty tophi without any apparent reason may disappear in one site and form in another. Tophi may become extensive and cause incapacitation in only a few years (Fig 20a, b).

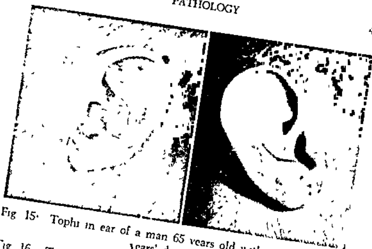


Fig 15 Tophi in ear of a man 65 years old with gout of twenty years' duration

Fig 16 Tophi in a Negro man 36 years old with gout of five years' duration

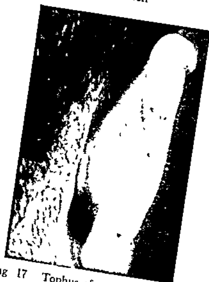


Fig 17 Tophus of gout behind ear



Fig 18A· Gouty arthritic deformities with tophi of both feet
B· Soft tissue tophi and bony destruction are evident



Fig 19 Olecranon bursa of a patient with gout for twenty years
Numerous large tophi fill the enlarged bursa

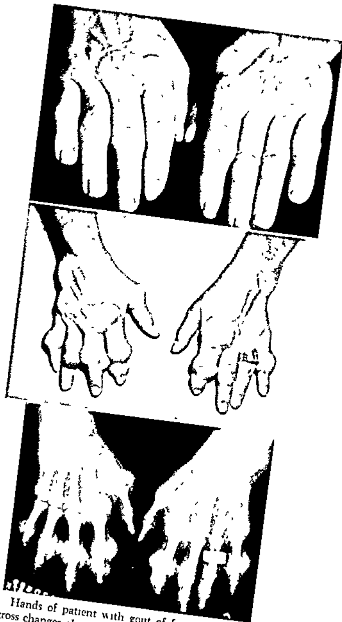


Fig 20A Hands of patient with gout of fourteen years' duration Slight gross changes about the left second interphalangeal joint
B Six years later This patient suffered numerous mild bouts of acute gouty arthritis while taking colchicine and aspirin (60 to 70 gr/day)
C. Roentgenograms of hands shown in B Note extensive tophaceous deposits about interphalangeal joints and typical bony changes

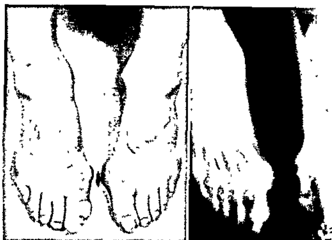


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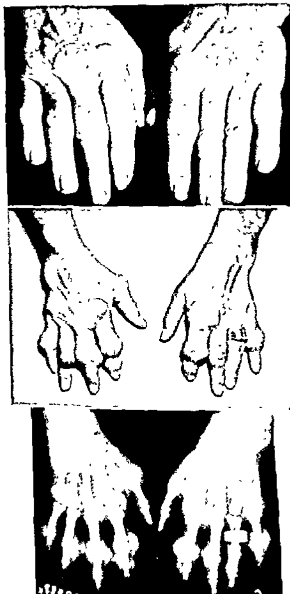


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B Six years later This patient suffered numerous mild bouts of acute gouty arthritis while taking colchicine and aspirin (60 to 70 gr/day)
C Roentgenograms of hands shown in B Note extensive tophaceous deposits about interphalangeal joints and typical bony changes

Uric acid tophi vary in size from minute deposits of uric acid crystals to masses several centimeters in diameter (Fig 21a, b) In large arthritis clinics usually one or two patients with long established gout have unusually massive tophi Joints with large deposits of urates less frequently become involved with acute gouty arthritis Usually the joints with lesser amounts of urate deposits are the sites of migrating acute gouty arthritis.

Small tophi about joints and on the ears (Fig 15, 16, 19) are pinkish yellow, non-tender and firm Tophi seldom become infected Associated infection, when present, may cause tenderness and an inflammatory reaction The overlying skin of large tophi is usually thin and pinkish yellow. If ulcerated, localized inflammation surrounds the ulcer, and fluid may be expressed from the lesion. The location of a tophus may cause mechanical limitation, and if ulceration is present, the added inflammation causes localized soreness and additional limitations. Sodium urate crystals can be expressed from the tophus, this material is chalk-white and as thick as toothpaste (Fig. 22). McCabe (213) noted that tophi contain 60 per cent urate, 30 per cent organic material and 10 per cent cations, chiefly sodium. It shows slim, needle-like crystals of sodium urate and some necrotic debris when examined microscopically

Fine, needle-like crystals are typical of urate deposits (Fig 23) However, Spitz and associates (310), in a report of cases of fatal gout, described another type of ura crystals in tophi of cartilage, bone and kidney obtaine from such a patient as "rhomboid in outline, doubly re fractive" showing "longitudinal striations" and occurring in "irregular clusters or sheaths of elongated needles." They were found to be insoluble in water, alcohol and weak acids (sodium citrate in formic acid) Formalin-





Fig 21A, B: Subcutaneous uric acid tophus removed from knee of a patient with long-standing gout.

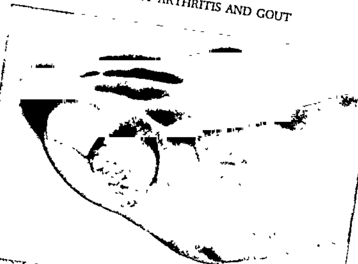


Fig 22. A draining uric acid tophus in the toe of a man with long-standing gout

Fig 23 Needle-like uric acid crystals taken from a gouty tophus (400 X).

fixed tissues imbedded in paraffin and stained with hemotoxylin-eosin showed the crystals, whereas the typical needle-like crystals of uric acid disappeared in similarly prepared tissues. Only their outline is left in the surrounding tissues. These observers suggested that the old urate crystals are water insoluble, whereas the rarer deposits are water soluble.

One would suspect that tophi would always be associated with hyperuricemia. However, a case has been reported of a Filipino man, aged 28 years, who had destructive gouty lesions, tophi and a repeatedly normal serum uric acid level (30).

Tophaceous gout is due to deposits of uric acid or salts of uric acid in osseous and soft tissue. An adequate explanation of the reason for its formation has not been given. Allbutt (4) maintained that urates of gout are never deposited in sound tissues. Because the upper limits of solubility of urates are not high, these salts may be precipitated in the tissues or joints. It is conceivable that trauma could result in increased flow of blood to the site, which may enhance deposition of uric acid crystals. Jones' (167) theory that the acute attack of podagra is associated with derangement of the arteriovenous periarticular plexus would be comparable with this reasoning. It has also been shown that the flow of blood is greater in the peripheral circulation of patients with gout (370). This feature is associated with the fact that the arteriovenous anastomoses are commoner in the more peripheral joints and may add somewhat to the explanation of the tendency of tophi to form peripherally. It has also been noted that during acute podagra, the blood flow in the foot is increased 600 per cent of normal and the dorsalis pedis and posterior tibial pulsations are of greater ampli-

two inches distal to the elbow joint, which is not a common site for gouty tophi (Fig. 25). When nodules are present in the olecranon bursa, it may be impossible on gross examination to determine whether they are rheumatoid nodules or urate tophi. A painless bursa that has been present only a few months and contains nodules is probably a rheumatoid nodule. Draining fistulas almost never develop in such nodules. Other subcutaneous nodules of rheumatoid arthritis may develop over the scapulas, spinous processes, sacrum and scalp, all uncommon sites of urate tophi. Nodules of rheumatoid arthritis on the fingers and toes may sometimes be difficult to differentiate from urate tophi. Usually the associated articular deformities and systemic symptoms will be sufficient to differentiate them from gouty arthritis. A nodule of rheumatoid arthritis on the helix of the ear may be differentiated from a urate tophus by the absence of urate crystals in such a lesion. If there is doubt about whether or not a lesion is a rheumatoid arthritic nodule or a urate tophus, biopsy is justifiable for histologic identification.

The nodules of rheumatic fever usually disappear after a brief period, and these nodules are only part of a clinical picture in which are usually found carditis, chorea and febrile rheumatic recurrence in addition to one or more of several minor manifestations (rash, epistaxis, precordial pain, fever, abdominal pain and pulmonary changes).

The nodules of sarcoidosis could be mistaken for the gouty tophus. Usually these occur at the sites of the interphalangeal joints. Rarely does the patient with sarcoidosis have acute incapacitating arthritis as does the patient with gout. Instead, they have arthralgia. Roentgenograms of the hands will show the characteristic lesions, or rarefaction, and punched-out areas in the

medulla of the phalanges without any periosteal change.

Xanthomas may sometimes be mistaken for gouty tophi, but the patient with these lesions is rarely troubled with acute arthritis that could be mistaken for acute gout.

Uric Acid Renal Calculi. In renal calculi the uric acid is most often in the pure state. Many uric acid stones are small and soft enough to pass the urinary tract without requiring surgical removal.

Renal calculi that are not pure uric acid stones are frequently combined with apatite and calcium oxalate monohydrate. A simple means of determining the true nidus of a renal calculus is not available.

Uric acid calculi may be small and pebble-like or shaped like a stag-horn. They are usually greyish brown but may be somewhat red (Fig. 26). Prien and Frondel (261) noted that "'brick-dust' precipitate from urine is pigmented uric acid." Uric acid apparently has a strong affinity for foreign pigments. The surface of the uric acid calculus is finely granular. In cross section the uric acid stone may have a fine, sandpaper texture of one color, or it may be ringed with alternating shades of brownish grey.

These stones are radiolucent and can usually be detected by roentgenography with contrast medium.

Uric acid sludge may fill the renal pelvis in such a manner as to hinder normal renal function, cause hematuria and be mistaken for a renal tumor. Such a case was reported by Kittredge and Downs (175) (Fig. 27a, b).

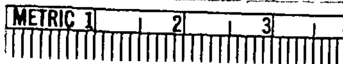




Fig 26. Uric acid stone removed from kidney shown in figure 35



Fig. 27. Retrograde pyelogram of a patient with gout who had attacks of renal colic and hematuria for many years. A Distended renal pelvis and dilated ureter on right. B. Correction of renal changes after therapy. Right renal pelvis and ureter were packed with uric acid sludge. Serum uric acid level 15 mg. per 100 ml.

Chapter V

CLINICAL MANIFESTATIONS

The clinical picture of gout varies from a mild chronic illness to an acute debilitating malady. Indeed, in a single person the clinical picture, during the course of the disease, may run the entire gamut of known signs and symptoms It can damage one or more organic systems, causing a wide variety of clinical changes These ramifications in the clinical manifestations can obscure the picture and lead to failure to make the correct diagnosis

Classical Gout. The classical portrait (Fig 28) of gout is well known to the medical historian but has seldom been reproduced in modern medical literature. It seems important that the student of gout be familiar with this original popular concept of the disease

The following composite clinical picture of classical acute gout will serve as an outline from which variations in the clinical theme may be developed. Typically, the patient is a corpulent white-collar worker in the fourth or fifth decade of life, and the father of two children He walks into the office with the aid of a cane or other support, his shoe has been cut to prevent pressure on his great toe (Fig 29); and he takes every precaution to avoid the slightest trauma to the painful joints or, if seen at home, he lies in bed or sits in a chair practically motionless, apprehensive, and anxiously protecting the red swollen joint Bed covers are carefully tented or the affected foot is uncovered He complains of having been



…g 28 A print (probably of the Rowlandson school) which …aphically depicts a patient suffering from an acute attack of gout … 29 Split shoes and cane are considered common apparel for men with gouty arthritis

awakened early by the sudden onset of severe pain He or his relatives may volunteer the diagnosis of gout because of youthful observation of the disease and familiarity with the family "gout stool"

When questioned, the patient relates that he had had two previous similar attacks of "arthritis" for which his physician gave him "pain pills" or cortisone. The two previous attacks lasted three and eight days, respectively, after which he was "completely well" The previous evening he had been aware of slight burning discomfort in the joint that is now the site of acute swelling and pain This is the first time he was aware of a "joint warning sign" prior to the acute attack He describes the discomfort as a steady, excruciating, localized pain that feels as if his toe were clamped tightly in a vise As in the two previous attacks, the present one developed after excessive eating and drinking Because of nausea, he has eaten nothing since the onset of the acute pain. There is no history of severe trauma to the involved area, but the patient has been on his feet more than usual The patient had previously had an attack of renal colic Several of his ancestors were known to have diabetes mellitus and a great uncle had gout. Obesity is a family trait and "rheumatism" is known to have occurred in several members of the family

Except for obesity and slight fever, the positive physical findings are limited to the involved joint The tarsophalangeal joint of one of the great toes is red, swollen, shiny, warm and exquisitely tender The joint is splinted because of the pain A papule 8 mm in diameter is observed on the left pinna This is presumed to be a tophus

The serum uric acid concentration is 7 mg/100 ml and the material expressed from the lesion on the ear proves to be sodium urate crystals Results of hematologic ex-



Fig 28 A print (probably of the Rowlandson school) which graphically depicts a patient suffering from an acute attack of gout.
Fig 29 *Split shoes and cane are considered common apparel for men with gouty arthritis.*

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amination are within normal limits, the sedimentation rate is slightly elevated, urinalysis reveals no abnormalities, and the blood urea nitrogen and fasting blood sugar values are within normal limits.

The patient is instructed to take colchicine (1/100 gr.) every two hours until abdominal cramps and diarrhea develop. This affords significant relief of pain, and administration of colchicine is discontinued after eight tablets have been taken Pain and swelling completely subside by the fifth day. The involved site is desquamated, and the patient considers himself completely well.

Initial Attack. The onset of gout is usually marked by acute monarticular arthritis. The first metatarsophalangeal joint is the site of the initial attack in 60 to 70 per cent of patients Other sites are the knees, ankles, dorsum of the foot, or possibly one of the joints of the hands or wrists, although any joint can be the site of the initial attack. Also, more than one site can be involved initially, as was the case in 53 of 242 patients with gout whom we questioned. Rarely, involvement tends to be migratory The attack can occur during any season of the year and any time of the day or night, although most patients experience their initial attack of gout in the early morning hours. This was true in more than half of the 280 patients with acute gout whom we studied

The pain may awaken the patient after a few hours of sleep or may develop during the day. The discomfort may not be evident while the patient is in bed, but only when he bears weight on the affected joint. Articular pain, which is usually excruciating, is the most frequent symptom. Initially, the pain may be mild to moderately severe, but within a few hours its intensity may increase in crescendo fashion to the point of incapacitation. In his dissertation on classical gout Jones (167) pointed out that

the patient with gout has "dreadful apprehension" lest someone jar him, or push the diseased foot The patient soon learns that the involved joint requires protection from even the slightest pressure Jones considered this feeling of dread characteristic of an attack of gout. The pain seems to be deep in the articulation, and has been described as burning, tearing, crushing, or knife-like. It maintains its apogee for hours or even days Usually relief of pain occurs in step-like fashion According to Rouché (278), Morris Longstreth in 1882 characteristically described this pain when he said, "Screw up the vise as tightly as possible, and you have rheumatism. Give it another turn and that is gout." Another graphic description of the pain Roueché attributed to Sidney Smith, an English clergyman, who said, "When I have the gout, I feel as if I was walking on my eyeballs" Possibly, this generation would deem it more fitting to visualize a rising mushroom cloud above the fission joint (Fig 30) rather than have it affected with a clawing, biting, stinging demon used to depict medieval podagra (Fig 31) The suddenness and severity of the initial acute attack frequently suggest to the patient the possibility of an insect bite (black widow spider, for example) or overlooked trauma On immediate inspection of the affected joint the patient seldom sees any significant sign Most of our patients related at least mild trauma to the involved joints, but it was not sufficient to be of great importance Initially, only slight swelling and tenderness may be noted, but within a few hours the benign looking joint becomes red or purplish, edematous and swollen, the skin over the exquisitely sensitive joint is warm, tight and sometimes shiny (Fig 32, 33). There is usually articular effusion, which is seldom detectable in the smaller joints but is more frequently demonstrable in the knees Commonly,



Drawing by Mrs Louis Loss

Fig 30. Atomic age concept of gout



Fig 31 Demon biting metatarsophalangeal joint (By James Billray (1757-1815), Philadelphia Museum of Art.)

Fig 32A, B Acute gouty arthritis in the left foot, note the edema chiefly over the dorsum of the foot

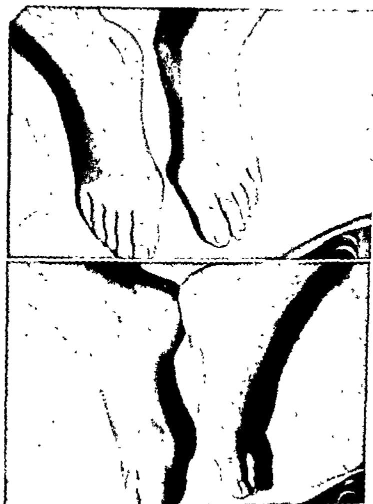


Fig 33A, B Acute podagra on right side, with redness, swelling and edema of first metatarsophalangeal joint and adjoining area in a man aged 39 years with polycythemia vera in whom gout subsequently developed

significant swelling extends beyond the margins of the joint and the appearance of the joint may suggest acute cellulitis

The initial attack may be associated with irritability, apprehension, anorexia and fever, which may rise to 102° F. Fever occurred in 15 per cent of our 280 patients during the acute attack of gouty arthritis Leukocytosis with slight left shift in the differential count, increased sedimentation rate and elevated serum uric acid level may be revealed in laboratory studies

The initial attack may last only one or two days, or as long as several weeks. The average duration is three to ten days Seldom does the patient recall any significant premonitory symptoms before the initial attack of gout As the acute attack subsides, the involved joint becomes less painful, swelling diminishes, redness fades, and only pitting edema remains at the site, which is no longer unduly tender Fever rapidly subsides The skin overlying the joint may become loose and desquamate (Fig 34, 35) The involved site may remain tender to pressure for a week or more after the other manifestations have subsided Shortly thereafter, the joint is completely asymptomatic

Chronic Onset. Sometimes patients are seen with chronic articular discomfort and even tophi Still others have chronic arthritis and have passed a uric acid renal calculus. Talbott (324) considered this to be common Patients with chronic arthritis who have supporting evidence of gout usually complain of aching of the feet, hips or back Seldom is a specific joint the site of the discomfort, usually patients complain of an entire area about an articulation The discomfort seldom requires anything more than symptomatic care Swelling does not occur It is only when acute, gouty arthritis develops with its more severe pain that the sufferer seeks specific therapeutic measures

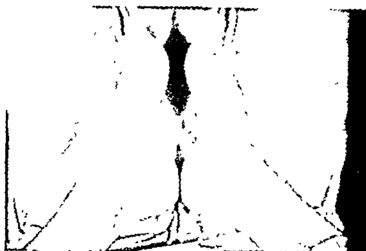


Fig 34 Subsiding acute podagra of patient shown in figure 33 Note subsidence of edema and desquamation

Of ninety-five of our patients with gout, five had a history of chronic arthritis prior to the acute attack There was no evidence of any other active arthritic process before the acute attack, and it is suspected that such patients experience chronic rheumatism which is in some way associated with gout. This chronic rheumatism usually does not inconvenience the patient after the onset of acute gouty arthritis.

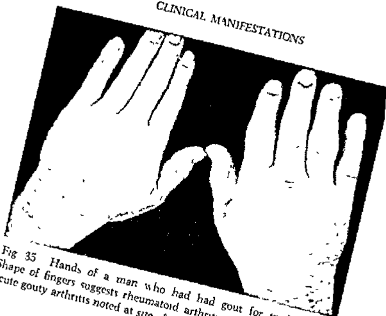


Fig 35 Hands of a man who had had gout for twelve years Shape of fingers suggests rheumatoid arthritis Desquamation after acute gouty arthritis noted at site of right third metacarpophalangeal joint

Recurrent Attacks. Although patients may experience only a single acute attack of gout, most patients have repeated attacks, this has led to consideration of gout as a chronic, recurring illness Of 240 patients with gout observed by us, only twenty-three had a single known acute attack, fifty had two or three attacks, and 167 had re-

peated attacks. In general, these patients reported increase in severity, frequency, and duration of attacks with passage of time During the first ten or twelve years, attacks of gout are mild. In rare cases, acute attacks of gout may be separated by an asymptomatic period of twenty to thirty years

With more recurrences of acute attacks, previously uninvolved sites become involved. It has been our experience that when the initial attack of gout occurs in the feet, the subsequent acute attacks often progress upward to the ankles, knees and upper extremities. Acute olecranon bursitis may be an exception to this. Involvement of the metatarsophalangeal joints, knees and ankles and feet follows most frequently. In our patients, the incidence of involvement of the right and left sides has been about the same. Acute gout in more than one joint simultaneously with a tendency to migrate from joint to joint may occur when therapy is inadequate.

During the early years, the acute recurrences are separated by completely asymptomatic intervals With increasing frequency and severity of attacks, residual stiffness and soreness of the previously acutely involved joints may occur and persist for long periods.

Recurrences may follow exercise, overeating, standing, an operation, or use of some medication Some recurrent attacks may be mild, but usually, if untreated, they become progressively worse. Rarely do untreated recurrent attacks of gout become less intense. Malaise, anorexia and irritability become more prevalent with each untreated recurrence

The symptoms and articular signs of acute, recurrent gouty arthritis are similar to those of the initial acute attack. Frequently, patients with acute, recurrent gouty arthritis become familiar with the "joint warning sign"

(353) or they become cognizant of some other premonitory symptoms. The most frequently mentioned premonitory symptoms are nocturia, polyuria, indigestion, anorexia and irritability. These were noted infrequently in the patients with gout that we questioned. Sixty of ninety-five of our patients detected a subjective reaction in the joint subsequently involved that forewarned them of the acute attack of gouty arthritis. They felt such sensations as burning, tingling, stiffness, warmth, numbness or awareness at the articular site. These symptoms were noted two to forty-eight hours before the acute classical pain appeared. This "joint warning sign" of gout has been useful in the diagnosis and prophylactic treatment of attacks (353, 355).

Interval Phase. The interval phase of gout is that period after the acute attack has completely subsided, when the patient has no arthritic residuals or articular discomfort. During this interval the patients proudly maintain that their joints are sound and asymptomatic, and that they carry on their usual pace of physical activity without difficulty. However, urinary calculi composed of uric acid crystals may become symptomatic during this interval phase of gout. The interval phase may last a few weeks or many years. During the asymptomatic period disregard for all dietary and physical precautions may not precipitate an acute attack of gouty arthritis in some patients. In a small percentage, though, such indulgence will frequently precipitate an attack. For unknown reasons, such recurrences of acute gouty arthritis are more prone to develop each spring and fall.

Chronic Gouty Arthritis. Repeated attacks of acute gouty arthritis usually result in articular damage, as well as chronic residual articular discomfort and progressive loss of normal articular function. The asymptomatic in-

Chapter VI

NONARTICULAR COMPLICATIONS

Most patients with gout are concerned chiefly with arthritis and tophi. However, gout may cause complications that can be of major importance

Renal. Renal damage is probably the most common and important extra-articular complication of gout. Gouty nephritis may be initiated by persistent albuminuria and casts, which may be detected even before appearance of articular symptoms, but these are usually found after repeated attacks of gouty arthritis. The early impairment of renal function may progress to loss of concentrating ability for solids, reduced phenolsulfonphthalein excretion of dye and later nitrogen retention There is apparently no characteristic pattern of renal damage associated with gout, although Modern and Meister (234) suggested that there are typical clinical characteristics that set the gouty kidney apart from other types of renal disease.

When Coombs and associates (75) studied renal function in 22 patients with gout, they concluded that most of the patients had evidence of some renal damage, the inability to concentrate solids being the earliest finding. With more impairment, tubular reabsorption of urates was reduced while the clearance was maintained They preferred to describe such renal dysfunction as "renal impairment of gout" rather than gouty nephritis. They suggested that renal damage from gout is irreparable but progresses slowly. However, reversal of impaired renal function in a patient was reported after probenecid therapy (256).

Gutman and Yu (140) noted essentially normal renal function in most of the 300 patients with gout they examined. The older patients with advanced disease had evidence of progressively declining glomerular filtration rate and tubular insufficiency

A gouty kidney can cause elevated nitrogen retention, which will persist for many years and eventually may be the primary cause of the patient's death Superimposed renal infection may alter the pathologic process and the clinical picture of the renal complication as well as the prognosis

Another phase of renal damage is formation of uric acid renal calculi Although a few (283) have expressed the opinion that nephrolithiasis occurs coincidentally with gout, the consensus is that such patients have a greater than normal incidence of renal calculi (176) Of our 280 patients with gout, fifty (17 8 per cent) had sufficient evidence for a final or tentative diagnosis of renal calculi Thirty-one of these patients (62 per cent) with symptoms of stones passed calculi Hematuria and renal calculi are common in this group of patients with gout, otherwise the general clinical characteristics of the patient with gout and stones seem no different from those of the patient with gout and no stones In patients in whom adequate studies could be done, it was concluded that most calculi passed were uric acid stones A patient with gout may pass a stone that appears to be an alkaline stone (calcium, et cetera), but its center could be a small uric acid nidus, which is the actual cause of the original development of the stone The uric acid calculus is usually small, smooth and round, may be soft, and is frequently passed so that operation is seldom necessary (5 to 14 per cent) We noted that in almost 70 per cent of our fifty patients with gout and stones renal symptoms were noted first

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Cardiovascular. Vascular sclerosis is probably present in all patients who have chronic gout. Schnitker and Richter (283) noted a higher incidence of vascular disease in patients with gout than in a control group. This vascular alteration occurs primarily in the kidney but is no different from vascular sclerosis in other parts of the body. Extensive arteriosclerosis is common in gout and usually is associated with generalized sclerosis of the larger vessels. According to Talbott (321), patients with gout have premature arteriosclerosis.

There was clinical or electrocardiographic evidence of cardiovascular disease in 39 per cent of our patients with gout. Serum uric acid levels have been reported to be higher in persons who have coronary disease before forty years of age (124). Peripheral vascular insufficiency is not commonly associated with gout; only about 4 per cent of our 280 patients with gout had peripheral vascular disease.

The incidence of hypertension in patients with gout is increased, although this association has not been stressed in the medical literature. Kuzell and associates (187) reported an incidence of 25.7 per cent of hypertension in male patients with gout and 35.8 per cent of their female patients with gout. In our 250 patients with gout 41.5 per cent had blood pressures above 160 mm. Hg. systolic or 100 mm. Hg. diastolic.

The incidence of arteriosclerosis with or without hypertension is greater in gouty patients than in controls and extensive sclerosis of the cardiovascular or cerebral circulation may be a contributing factor in the cause of death in these patients. Like diabetes mellitus, gout is a metabolic disturbance and because at necropsy joints are rarely examined, the sclerotic organs that contribute primarily to death are labeled cause of death, so that the

true morbidity of cardiovascular disease due to gout is unknown at present

We noted that patients with gout and elevated blood sugar levels had a higher incidence of arteriosclerosis compared with patients with gout having normal blood sugar levels. Despite the prevalence of obesity in patients with gout, concurrent clinical diabetes mellitus is uncommon in these patients, although as mentioned previously, a family history of diabetes is frequently obtained from the gouty patient. Necropsy observations in two patients with gout were reported (340), in which urates were found in the arteries and organized thrombi and in the valves and muscles of the heart.

Ophthalmologic. Acute episcleritis, anterior or posterior scleritis, tenovitis, keratitis and conjunctival tophi are some of the ocular changes reported in patients with gout. The pathogenesis of such processes is not fully known. Fortunately, these complications are not common but they should be kept in mind when patients are found to have gout It is of interest that in the past ocular symptoms of gout gave rise to a condition called the "hot eye of gout," which implied an inflamed conjunctiva associated with a sensation of heat in the orbit and a scratchy feeling in the lid, that lasted a few days and possibly terminated in iridocyclitis The condition was usually associated with the interval phase of gout (163, 178, 217, 377)

Miscellaneous. Kuzell and coworkers (187) reported an impressive incidence of 27 per cent of hypothyroidism in 504 patients with gout The criteria for this evaluation were not given We believe that a diagnosis of hypothyroidism cannot be made in the absence of myxedema and we have observed myxedema in less than 1 per cent of patients with gout Published information is meager in this regard

Chapter VII

LABORATORY OBSERVATIONS

PROPER determination of the uric acid content of body fluids is difficult. It requires meticulous attention to detail and frequent restandardization. However, it is still the most useful laboratory test in gout.

The uric acid level is determined in many clinical laboratories by the methods of Folin and Denis (110), Benedict and Behre (25) or Brochner-Mortensen (45). The first two methods depend on the color resulting from reduction of the complex tungstate whereas the third depends on reduction of potassium ferrous cyanide. These levels are not quantitative, since other plasma constituents are responsible for some of the color change. With the methods of Folin or Benedict the serum uric acid levels usually vary from 3 to 5 mg./100 ml.; with the Brochner-Mortensen test the level is slightly higher. The upper normal level of serum uric acid for men is 1 mg. higher than for women (387) In our laboratory, the upper limit of normal is 6 mg. per cent for men and 5 mg. per cent for women. This difference apparently develops after puberty, since it does not occur in prepubertal children (372).

The technics of determination of uric acid in the blood and urine have been well described by Yu and Gutman (387). Serum uric acid determinations are preferable to those of whole blood (29) The uricase method of determining the serum acid level reduces the effect of nonspecific factors in the conventioual colorimetric tests

(100) Because enzymatic estimation of serum uric acid is complex and expensive, there is little indication for its use in general practice

In the absence of advanced renal disease, the level of serum uric acid does not indicate a particular phase of the gouty process Serum uric acid levels have often been normal during the first attack of gout, the reason for this may be that the patient is taking a drug that has uricosuric properties The urates in blood are equally distributed between the plasma and cell Precipitation of the serum protein often carries down some of the uric acid, this would account for the low estimate of the amount present The direct methods have additional difficulties in that normal blood constituents, such as ergothionine, glutathione, other reducing substances, and many phenolic substances, also give a deep blue color with the reagent, whereas amino acids and other unknown substances of plasma interfere with color development Since the serum uric acid level is often within normal limits, particularly during the first attack of gout, it is unwise to exclude the diagnosis of gout on the basis of a single normal value.

The blood urea nitrogen level should be determined when the serum uric acid is measured Azotemia, when present, is accompanied by an elevated serum uric acid level Increases in the serum uric acid level may also result from polycythemia vera, leukemia, lymphoma, myelofibrosis, pernicious anemia and severe acute infections Dubin and associates (91) observed hyperuricemia in seven of eleven patients with hypoparathyroidism, and this elevation appeared related to the derangement of phosphorous metabolism, probenemid corrected the alteration Hyperuricemia is sometimes found in patients with arthritis associated with psoriasis (387) and in some pa-

tients with rheumatoid arthritis (203, 327). Serum uric acid values as high as 36 to 38 mg./100 ml. have been observed in patients with lymphoma (349).

Use of pyrazinamide will cause hyperuricemia with associated decrease of 30 to 50 per cent in urinary excretion of uric acid (77). Aspirin and sodium salicylates seem to block this action of pyrazinamide (292). Chlorothiazide (Diuril®) has been found to produce significant elevation of the serum uric acid level (188a) and in some patients this was associated with articular pain (244a).

The serum uric acid level may be lowered by use of uricosuric agents, such as large doses of salicylates, probenemid, phenylbutazone or cortisone Zoxazolamine is now recognized as a potent uricosuric agent. Impairment of renal tubular reabsorption is also associated with reduction in the serum uric acid level (40). If a true level of uric acid is desirable for aid in diagnosis, use of all uricosuric agents should be discontinued for at least two days before the test is done. Use of colchicine need not be stopped, for it does not influence the serum uric acid level. Small doses of salicylates, for unknown reasons, probably cause uric acid retention with hyperuricemia.

Limited observations (225) have indicated that estimation of the daily blood level of uric acid of patients with gout may result in three types of curves: 1) hyperuricemia with a fluctating high level, 2) varying amounts of hyperuricemia at around the upper limits of normal, and 3) normal serum acid levels Talbott (324) mentioned that he had never observed a patient with gout in whom the elevated uric level became normal and remained so without the influence of uricosuric agents.

The red blood cell count is usually normal in primary gout Since gout can be secondary to blood dyscrasias, it

is imperative that adequate hematologic studies be done on all patients with gout (181, 188).

Anemia is never associated with the initial phase of uncomplicated gout and is rarely present in the later stages Paper electrophoresis studies of the hemoglobin of eight of our patients with gout failed to reveal any abnormalities. One case of gout was reported in a man seventy-nine years old with homozygous hemoglobin C disease (264) Leukocytosis is generally associated with acute gouty arthritis The sedimentation rate is frequently elevated during the acute attack of gout and is increased at least threefold in half of the patients It usually returns to normal shortly after the acute stage has subsided If it remains elevated after the articular symptoms have subsided, one must be alert to some other involvement, such as rheumatoid arthritis

In our patients with uncomplicated gout hepatic function was normal, as were the serum protein and cholesterol levels However, total cholesterol values have been reported by others (371) to be high just before the onset of gouty arthritis and lower in interval periods

The fasting blood sugar levels appear to be elevated more frequently in patients with gout than in controls, but whereas this increase is significant, it is seldom associated with diabetes (356)

The blood urea nitrogen level is elevated only after considerable renal damage has occurred, and this is usually a late manifestation of severe gout Terminal uremia may not occur for years after renal impairment has become fixed

Serum transaminase levels were elevated in some of our patients during acute attacks of gout (354) These patients did not have laboratory evidence of hepatic disease or active myocardial damage. Uric acid levels did

not parallel the serum transaminase levels or drug therapy (Fig 36) The significance of this observation remains to be clarified. This elevation of the transaminase level could be confusing in a patient with myocardial damage and gout. In such a case it may be difficult to determine whether a patient should be allowed more physical liberties for fear that the elevated transaminase level may indicate continued myocardial damage. Barr and coauthors (13) reported little variation in the average serum transaminase titers in patients with gouty arthritis but they did not indicate the stage of the gout.

Early in gout result of urinalysis is usually normal. Mild albuminuria may be the first sign of renal involvement. Only seven of 202 of our patients with gout had sufficient urinary evidence to suggest renal disease other than stones Hematuria and passage of uric acid sludge or stones may occur, and have been discussed in more detail under the section on the Kidney in Gout (pg 35).

The twenty-four hour concentration of uric acid in the

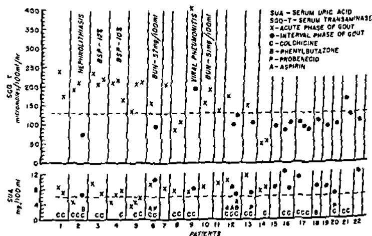


Fig 36: Serum transaminase levels in gout.

urine may be helpful in determining increased urinary output of urates. However, correct determination of this level is troublesome and is not available in all laboratories. The normal person on an average diet excretes about 700 mg of urinary uric acid daily (range 500 to 1000 mg /24 hr.) (318). This may be reduced to 200 or 300 mg /24 hr on a restricted purine intake Usually the basal excretion of urinary uric acid of patients with gout is normal but 25 per cent of gouty patients have increased excretion of urinary uric acid Futcher (119) observed decreased excretion of urates before onset of acute symptoms of gout It has been observed that the true urate concentration in the cerebrospinal fluid is only 6 per cent of that in plasma (369).

Tophi may be aspirated if the diagnosis is in doubt and the aspirated material examined microscopically for needle-like crystals or subjected to the muroxide chemical test.

Search may be made for urate deposits in synovial membranes by surgical biopsy of the joint or joint punch biopsy (392) Tissue so removed should be preserved in absolute alcohol but urate deposits have been found in specimens preserved in formalin The value of this means of diagnosis is limited but at times extremely important

Study of synovial fluid is occasionally helpful in differentiating gout from traumatic arthritis or osteoarthritis (274) Synovial fluid from an acute gouty joint is usually turbid, contains an increased number of leukocytes (average 10,000 to 15,000 up to 70,000 per cu mm with polymorphonuclear leukocytes predominating), has reduced viscosity, and usually forms a poor mucin clump when precipitated by 1 per cent solution of acetic acid

Chapter VIII

ROENTGENOGRAPHIC OBSERVATIONS

No radiographic alterations may be detected in the joints of patients with gout initially or even after many years of recurrent attacks of acute gouty arthritis Frequently, however, recurrent gouty arthritis is associated with roentgenologically demonstrable structural changes *in the soft tissues, joints or bones. About one-third* of the patients with gouty arthritis have characteristic roentgenographic changes in the later stages of the disease and another third exhibit changes compatible with, although not typical of, gout. It is not known why some persons with relatively severe, recurrent gouty arthritis escape significant articular damage.

As early as 1896, von Huber (161) reported roentgenographic changes in the hands of a sixty-one-year-old man with gout and discussed some differential diagnostic features. *He described the lesions in the bones as "bubble* shaped," at times more descriptive than the currently overused term, "punched-out." Later, radiographic studies refined our knowledge of the progressive manifestations of gout and they now afford considerable assistance in the study of these patients (214, 215, 276, 334).

The most commonly involved joints are those in the feet and hands, followed in order by the wrists, knees and elbows However, any joint may be involved Bilateral involvement is occasionally discovered but it is almost never symmetrical.

The earliest demonstrable radiographic changes are

swelling of soft tissue and loss of marking of the fascial planes overlying a normally appearing joint (Fig 37) The swelling is an acute, diffuse, peri-articular manifestation, if recurrent and asymmetrical, it should suggest the diagnosis of gout Pugh (262) stressed the fact that this finding is not diagnostic and may be better evaluated clinically than roentgenographically Similarly, observation of fascial plane markings is difficult to evaluate and rather unreliable as a diagnostic aid

Development of osteoporosis in gout is another difficult feature to evaluate objectively, particularly because of the wide variation in normal and the recognized difficulty of controlling technical factors in roentgenography We judged that some degree of osteoporosis was present in 70 per cent of our 280 patients, about twice the incidence reported by Taylor and coworkers (334) The change is usually only local or regional (Fig 38) It is rarely as severe or as generalized as in rheumatoid arthritis, and is usually more pronounced than in osteoarthritis

In more advanced cases, a series of progressive changes occurs in those areas in which tophaceous deposits are enlarging These usually involve the bones at the articular surfaces In an excellent study, Rosenberg and Ahrens (276) described the earliest osseous manifestation as "a zone of osteoporosis on the medial aspect of the base of the first metatarsal bone and the first phalanx" (Fig 39) This zone of osteoporosis later appears frankly "cystic" If a thin rim of cortical bone remains over the surface of the lesion, a "bubble shaped" radiolucent lesion is produced (Fig. 40), as was the case in 61 of our 280 cases If the normal outline of the cortical bone is disrupted, a notched type of defect is the result and this apparent absence of bone has led to the descriptive term of "punched out area" (Fig 41). A recent report by Bartels





Fig. 37. Roentgenogram showing periarticular swelling of soft tissue at metatarsophalangeal joint of great toe, with no evidence of destruction of bone.

Fig 38: Localized osteoporosis on the right (left in picture) with gouty changes at metatarsophalangeal joint of great toe.



Fig 39 Zone of osteoporosis at base of proximal phalanx

(16), however, urged reappraisal of the notion that the bone has been destroyed in these locations, for his experience (with roentgenologic proof) indicated that the bony architecture and contour may be restored after adequate modern therapy. This evidence suggests that the bone is not always destroyed in a punched out area but at times is only considerably decalcified or replaced by relatively radiolucent tophaceous material The tophi are known to be composed of uric acid crystals, and these are





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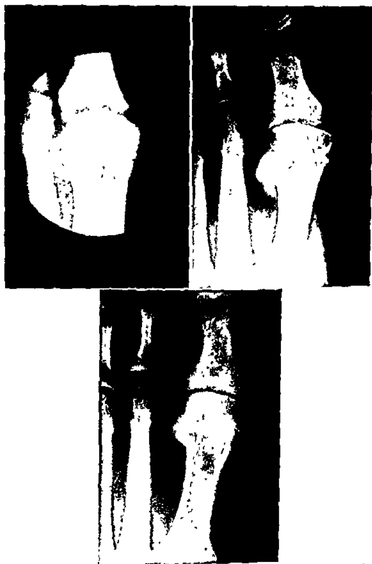


Fig. 40. A *(Upper left)* "Bubble-shaped" lesion of medial side of head of first metatarsal bone B *(Upper right)* "Bubble-shaped" cystic lesion in head of first metatarsal bone. C. *(Lower)* "Bubble-shaped" or cystic lesion in head of first metatarsal bone

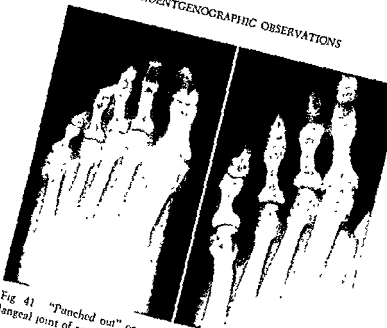


Fig 41 "Punched out" or notching type lesions at metatarsophalangeal joint of small toe Small notch at base of proximal phalanx and larger one at head of metatarsal bone

Fig 42 Irregular destruction of articular surfaces of second metatarsophalangeal joint Note absence of osteoporosis Head of fifth metatarsal bone shows gouty changes

radiolucent as compared with the osseous tissue that is replaced

As the radiographic changes become more pronounced, the manifestations of marginal articular destruction increase Not only is the corner of the metaphyseal bone lost, but the articular surface becomes irregular, faint, or increasingly destroyed (Fig 42) The articular space is narrowed, disorganized, and finally not visualized (Fig 43) Constant use of the joint at this stage apparently results in further disorganization and development of



Fig 43 Multiple joints of hands and wrists show various stages of destructive effects of gouty arthritis

Fig 44 Note secondary marginal osteophytes after gouty arthritis has largely destroyed articular surfaces (distal interphalangeal joints of middle and ring fingers)

secondary hypertrophic changes, such as marginal osteophytes (Fig 44) These appeared in 102 of our 280 patients Detached spicules and fragments of bone are suggestive of traumatic osseous debris.

Many years ago McCarty (214) pointed out that both destructive and proliferative manifestations may be evident in radiographic studies of the joints in gouty arthritis Eventually the joint in chronic gouty arthritis presents a striking appearance it is completely disorganized, with formless masses of tophaceous material, fragmented remnants of the articular cortex, irregularly eroded and deformed bones, and haphazard alignment and hypertrophic changes (276) Soft tissue deformity, calcareous material, and the clefts of draining sinuses may complicate the picture (Fig 45). Ankylosis is rather infrequent (208).

Tophaceous deposits do not necessarily involve only the articular surfaces (198) Urate deposits in or beneath the periosteum adjacent to the shaft of the bone produce a notching type of erosion near the end of the shaft These are most often seen in addition to the articular changes but may be the first radiographic change to attract attention (Fig 46). At the edges of these expanding lesions along the shaft or articular margins, spur-like projections may develop and increase to the point of producing a "basket weave overlay," in the words of de Lorimier (83)

Similarly, tophi developing in cancellous subchondral regions of the metaphysis or in the medullary canal result in a rounded, sharply defined, radiolucent shadow (Fig 12) When small, these "cystic" lesions may mimic changes found in other types of arthritis However, they are frequently larger than 5 mm in diameter, unlike



Fig 45· Advanced gout has completely disorganized metatarsophalangeal joint of great toe Note also notching defects at base of first metatarsal and head of fifth metatarsal bones

Fig 46 Medial side of shaft of first metatarsal bone shows notching type of erosion "Basket-weave overlay" is rather suggestive Large, soft-tissue tophus and sharply defined notch at base of proximal phalanx are prominent

similar shadows in rheumatoid arthritis, and are usually not surrounded by a zone of sclerosis, as in osteoarthritis

An unusual manifestation, noted by Rosenberg and Arens (276) is expansion of the end of a bone, resulting in a radiographic appearance similar to that produced by primary bone tumors (as chondroma, giant cell tumor and sarcoma) An entire bone may be destroyed and leave only bony fragments in the area (Fig. 47).

Another unusual manifestation is development of extensive changes in the spinal column (Fig. 48). In the





Fig 47 Localized advanced gout has expanded and largely destroyed shaft of distal phalanx of second toe

Fig 48 Alterations in bodies of fifth and sixth cervical vertebrae are consistent with tophaceous changes, in patient with chronic advanced gout Disk narrowing and osteophytosis are also present

case recorded by Ludwig and coauthors (208), these advanced to the state of simulating ankylosing spondylitis, such as in rheumatoid arthritis In Kersley and coworker's (173) remarkable case, the vertebral involvement led to extreme softening of the cervical vertebrae with resulting subluxation

Secondary deposition of calcium in a tophus renders the lesion opaque to roentgen rays (187) Calcareous tophi produce a spectacular appearance in roentgenograms, especially if the tophus is large or if multiple areas of involvement are discovered (Fig 14). A recent report by Lichtenstein and coworkers (198) illustrates an extreme example in which white, chalky-appearing tophi were

seen in many locations. Their case exemplifies the fact that not only may the synovial membrane and articular cartilage and bones be involved, but regional tendons, ligaments and bursa may exhibit tophaceous deposits (304).

Extraskeletal involvement by gout deserves brief mention Theoretically, tophi may appear in almost any tissue. Roentgenologically, such tophi will not be visualized unless there is a tumefaction of the subcutaneous soft tissues (Fig 49). One exception is in the urinary tract, where tophaceous calculi may be visualized by contrast methods despite the radiolucency of the uric acid stone (Fig 50) Among our 50 patients with gout who were examined urographically, 6 4 per cent had roentgenographic *evidence of urinary calculi* In advanced cases severe renal damage may prevent adequate visualization by excretory methods



Fig 50 Retrograde pyelogram shows a large radiolucent stone filling pelvis of right kidney. Calyces are blunted and a smaller stone lies in inferior calyx



Fig. 51. Roentgenograms showing changes during a period of twenty years in bones and joints of patient with gout A. B Foot C. D. Knee

Roentgenologic findings do not permit differential diagnosis in many cases (262, 334). The evidence obtainable from roentgenograms is reliable, however, especially when appraised in the light of clinical and laboratory observations and time (Fig. 51, 52). It must always be appreciated that changes similar to those produced by gout may occur in rheumatoid arthritis, osteoarthritis, sarcoidosis, myeloma, metastatic malignant disease, hyperparathyroidism, tuberculosis and syphilis, and perhaps other diseases.

Talbott and coworkers' (332) observations on a magnification technic for the roentgenographic study of osseous gout are of interest. Unless special, rather expensive x-ray equipment is available, attempts to magnify gouty lesions in bones will usually result in loss of detail and are of little value diagnostically. Roentgenograms are helpful in direct proportion to the intelligence and understanding with which they are analyzed.



Fig 52 Hand of patient with chronic gout The changes at the proximal interphalangeal joints were rather suggestive of rheumatoid arthritis Note absence of bony atrophy or marginal destruction

Chapter IX

DIAGNOSIS

The diagnosis of gout should not be difficult to make even before the classic features develop. Repeatedly, however, patients with gout have related that the disease was not recognized until their third or fourth acute attack. The need for a specific diagnosis is imperative for proper management of these patients. The clinician should be aware that the clinical picture may vary from mild monarticular arthritis with hyperuricemia to a severe, crippling articular disease. The general use of steroids and ACTH for all types of nontraumatic articular swelling will deter the early diagnosis of gout.

The diagnosis of gouty arthritis in any medical center depends directly upon the interest and index of suspicion of the attending staff. The family of the patient with gout is sometimes the first to venture the correct diagnosis. The clinician should always rely on the history, physical findings and laboratory data for diagnosis. In each, certain characteristics serve as useful diagnostic guides. Frequently, the attacks occur in the early morning, after a stressful surgical procedure, during a trip, or during the holiday season. They may follow administration of some drugs, such as insulin, ergotamine tartrate, liver extract, mercurial diuretics (260), Decholin,'s thiamine chloride (345), steroids or ACTH (271, 302). Considerable loss of weight as a result of severe dieting may be the forerunner of an attack of acute gout.

The severe articular pain may be preceded by sensa-

tions, such as burning or tingling of the joint, with development in several hours of exceptionally severe pain, swelling, redness and edema. Desquamation may occur at the site of inflammation after the swelling subsides.

The diagnosis should be strongly suspected if the attack is relieved dramatically by an adequate amount of colchicine. Complete alleviation of articular and systemic symptoms between attacks of acute arthritis should lead to the suspicion of gout. The presence of acute olecranon bursitis or Achilles tendonitis suggests gout as well as a history of chronic nephritis or renal calculi

Gout should be suspected in a patient with acute arthritis and a family history of gout or diabetes mellitus The diagnosis should also be suspected in a plethoric, obese man with acute monarticular arthritis who appears exceptionally well, has an atmosphere of tension or apprehension and fearful protection of the involved site, is unable to bear weight on the lower extremities, uses a cane and wears a split shoe or slipper. If monarticular arthritis is associated with a peri-articular fistula, gout should be considered as a diagnosis.

Among laboratory diagnostic aids is elevated serum uric acid level A blood count compatible with a diagnosis of blood dyscrasia may arouse suspicion of the diagnosis Demonstration of punched-out or "bubble shaped" lesions in roentgenograms of the involved joints aids in the diagnosis Demonstration of urate deposits in synovial membranes and tophi in histologic sections or smear is conclusive.

To recapitulate, the diagnostic criteria of gout may be listed as follows.

History

Gout should be suspected when:

1) Unexplained acute monarticular arthritis occurs in any male

2) There is a history of mild trauma of the joint prior to the acute arthritis, such as walking excessively.

3) Arthritis begins suddenly during a trip, holiday season or after a banquet.

4) Articular swelling and pain develop suddenly in the early morning

5) Acute arthritis follows an operation or use of medications

6) The patient notices sensations (burning, etc.) preceding the onset of pain in the joint ("joint warning sign")

7) Acute monarticular pain is of exceptional severity

8) Severe articular pain develops within a few hours

9) Previous renal colic or passage of renal stones has occurred

10) Previous similar attacks of arthritis were relieved dramatically by colchicine.

11) Previous similar attacks of arthritis lasted ten days to three weeks and then completely subsided without residual

12) Acute arthritis and fever occur in an otherwise healthy male

13) Acute arthritis occurs during or after severe dieting and loss of weight.

Family History

1) Gout

2) Renal stones

3) Diabetes mellitus

Physical Examination

1) Plethoric, obese male who appears well but who had monarticular arthritis.

2) Apprehensive attitude of protection of the involved joint.

3) Inability of the patient to bear weight or stand on an involved joint of a lower extremity.

4) When the patient uses a cane, crutch or split shoe after only a few hours or days of illness.

5) In a male patient with a red, swollen, exquisitely tender joint (great toe, foot, knee or ankle).

6) In any patient with tophi or periarticular fistulas

Laboratory Data

1) Elevated serum uric acid level with a normal blood urea nitrogen level.

2) Polycythemia vera, leukemia or other blood dyscrasias are associated with arthritis.

3) Roentgenographic demonstration of a bubble-shaped area in the osseous structure involved.

4) Urate deposits can be demonstrated in synovial membrane or uric acid from tophi.

These are the diagnostic landmarks in typical acute gouty arthritis Like all diseases, the clinical picture varies often enough for the clinician to be aware of the less typical types of gout and the differential diagnostic features Provocative tests with certain food and port wine have been reported unsuccessful as diagnostic aids (19, 20, 151).

DIFFERENTIAL DIAGNOSIS

In the differential diagnosis of gouty arthritis several conditions must be considered. *Rheumatoid arthritis,* which may involve only one or two joints initially, can be confused with gout (350). It is usually atypical rheumatoid arthritis with sudden onset and severe pain in the joint. Important differential points in gout and rheumatoid arthritis are that gout is unusual in the menstruating woman, and rheumatoid arthritis is characterized by bilateral, symmetrical, progressive involvement of joints associated with lassitude and fatigue. Involvement of the proximal phalangeal or temperomandibular joints, especially early in the disease, is more suggestive of rheumatoid arthritis than gout. In approximately [illegible] per cent of patients with rheumatoid arthritis the onset is atypical, and in half of these the clinical course can be confused with gout. Such patients have recurrent acute attacks of arthritis with apparently complete remissions, which become increasingly shorter, giving way to the typical picture. A family history of gout or diabetes mellitus suggests gout rather than rheumatoid arthritis. A nodule can be differentiated only by microscopic examination (see section on tophi). Roentgenographic demonstration of a punched-out bony lesion is not necessarily diagnostic of gout, and when combined with destruction of bone, extensive osteoporosis and narrowing of the articular space, is more frequently associated with rheumatoid arthritis. Chronic gouty arthritis with unusual ankylosing deformities can even more closely resemble rheumatoid arthritis (208). In two such cases the presence of tophi, hyperuricemia and long-range observation aided in diagnosis. Such cases are rare. Both gout and rheumatoid arthritis can occur in the same patient, but the diagnosis of these

two diseases is usually made only after a long period of observation.

Palindromic rheumatism, with its acute arthritic flare-ups that last for a few days and have no associated residuals, occurs frequently in middle-aged men and can cause diagnostic confusion Repeated normal uric acid levels, and failure to prevent attacks with continuous administration of colchicine will probably exclude most cases of gout that could be mistaken for palindromic rheumatism As the acute arthritis frequently subsides within seventy-two hours, the patient seldom has an opportunity to evaluate a full course of colchicine.

Acute rheumatic fever with limited articular involvement may simulate gout. The sudden onset of symptoms is common in both. However, gout usually causes more severe pain and less febrile reaction than does rheumatic fever Cutaneous and subcutaneous lesions associated with nosebleeds and sore throat are not encountered with gout. Electrocardiographic changes and cardiac disease, when present, support the diagnosis of rheumatic fever. An elevated serum uric acid level is not expected in rheumatic fever.

Acute postoperative phlebitis in the region of the foot or ankle may be difficult to differentiate from gout It usually occurs four to ten days after operation Its occurrence after an operation, the associated pain and the mild favor may add to the confusion Palpation of the venous trunk at the site of inflammation is the most helpful diagnostic physical aid in differentiating phlebitis from acute gouty arthritis Hyperuricemia is a major diagnostic aid favoring gout Rarely, Buerger's disease has been confused with gouty arthritis, but differentiation should not be difficult

Psychogenic rheumatism is seldom a diagnostic problem, for these patients usually have a more chronic type of arthralgia, the pain, which is frequently continuous, is not as intense, and there is no associated swelling

Patients with **acute bacterial arthritis** are rarely encountered in private practice but cause some concern in the larger charity medical centers The condition can be confused with acute gouty arthritis **Gonococcal arthritis** or infectious arthritis is frequently polyarticular in the early stages, and then becomes monarticular Demonstration of the organism in the primary site is an early differentiating aid Purulent fluid in the joint carries almost equal diagnostic weight. Examination of the fluid in the involved joint is indicated when the diagnosis is questionable Prompt favorable response to administration of antibiotics should suggest bacterial arthritis, especially if there has been recent exposure to the Neisserian infection **Tuberculous arthritis** is usually chronic or subacute and the clinical picture and roentgenographic changes are different from those seen in acute gouty arthritis.

Osteoarthritis may be confused with gout when an interphalangeal joint that is the site of a Heberden's node becomes acutely involved The location, evidence of osteoarthritis elsewhere, and the fact that the condition usually occurs in female patients are helpful in the differential diagnosis Rarely does osteoarthritis cause acute symptoms with the severe pain that is associated with gout Osteoarthritis in the weight-bearing joints of an obese patient who has traumatized one of these joints may result in acute arthritis that can be confused with acute gouty arthritis The usual site is the knee Usually the pain is not as severe as that associated with gout, and rest and heat afford relief The history of trauma and

evidence of osteoarthritis in other joints, in the presence of normal serum uric acid level, are helpful aids.

Patients with **collagen diseases** other than rheumatoid arthritis and rheumatic fever frequently seek medical attention because of swollen painful joints. Gout can be excluded usually on the basis of a history of insidious onset, polyarticular distribution, and systemic symptoms not characteristic of gout.

An acute serum sickness reaction or **acute sensitivity reaction** could be sudden in onset and associated with acute articular swelling and pain. Usually the pain is not intense and is associated with other features of the allergic reaction. History of recent exposure to such a causative agent is a major differential point.

Intermittent **hydroarthrosis** may be temporarily confused with acute gout. In this condition either knee is the site of trouble, there is no increased warmth of the joint, the attacks are periodic (seven to eleven days between attacks), there are no constitutional symptoms and the serum uric acid level is normal.

Acute hypertrophic pulmonary osteoarthropathy will result in a swollen, painful joint, but the onset of symptoms is more insidious, the pain is less severe, usually involvement is bilateral and symmetrical, and clubbing of the fingers and toes is present. Roentgenographic periosteal elevation in one of the long bones will confirm the diagnosis. A primary malignant growth in the joint should seldom be confused with gout. The insidious onset and roentgenographic evidence would probably exclude the diagnosis of gouty arthritis.

Acute bursitis associated with a hallux valgus deformity may be mistakenly diagnosed as gout. In these cases swelling is usually limited to the bursa, and the metatarsophalangeal joint can be moved within a limited range

without undue pain In acute bursitis elsewhere, the final diagnosis rests on the site of involvement, roentgenographic evidence and serum uric acid levels.

In many patients the diagnostic differential findings necessary to establish or exclude the diagnosis of gout may not be available or adequately demonstrated In such patients if there is no contraindication to the use of colchicine, its administration in adequate doses will be a most valuable aid in the differential diagnosis of gout.

Chapter X

ASSOCIATED DISEASES

Gout may be associated with other diseases or their treatment, or it may occur concurrently. The blood dyscrasias (secondary gout) are the disorders most frequently associated with gout. Other conditions that have been associated with gout are diabetes mellitus, lead intoxication, hypercholesterolemia, osteitis deformans, essential lipemia, pseudo-pseudohypoparathyroidism and Morgagni-Stewart-Morel syndome.

SECONDARY GOUT

Hyperuricemia, which is the keystone of gout, occurs frequently in patients with certain blood dyscrasias, and such patients occasionally have overt gout (14, 188). Gout occurs most often in association with primary polycythemia and myelosclerosis, and less commonly with chronic leukemia, pernicious anemia, hemolytic anemia, secondary polycythemia, Cooley's anemia and malignant lymphoma The simultaneous occurrence of these blood dyscrasias with gout is considered to be greater than by chance alone. Although hyperuricemia occurs in patients with chronic nephritis and multiple myelomatosis, seldom do these patients have gout.

POLYCYTHEMIA VERA

In 1914, MacCormac (210) reported a case of gout and polycythemia. Similar reports of increased endogenous uric acid excretion in polycythemia followed (164,

293). The incidence of polycythemia with hyperuricemia and gout is reported to be between 5 and 10 per cent. The familial tendency to gout is slight in these patients, and more females are afflicted than in primary gout (80, 277, 339, 342, 384) Tinney and associates (339) found eight cases of gouty arthritis among 168 patients with polycythemia and Videbaek (342) reported eleven in 125 We have seen twelve patients with gout and associated blood dyscrasia, six of which were polycythemia. In eight of eleven of Videback's patients the gout antedated recognition of the polycythemia by two to thirty-six months. Whether such cases are truly cases of secondary gout or are independent diseases is not certain. The clinical picture does not differ in any discernible way from that of patients with primary gout.

Opsahl (244) noted that eight types of anemia are associated with hyperuricemia during the reticulocyte response A depressing action on the increased endogenous uric acid production caused by a drug, such as phenylhydrazine, will reduce the quantity of serum uric acid formed (293). It has been shown that venesection of dogs actually results in a rise in their endogenous uric acid owing to the increase in formation of red blood cells (180). Wintrobe (365) pointed out that in typical cases of primary polycythemia the blood uric acid level is usually normal

The interesting but limited studies of Yu and coworkers (390) on the biosynthesis of uric acid from glycine N^{15} in patients with polycythemia and gout demonstrated a slow rise of glycine-N^{15} incorporation into uric acid in gout secondary to polycythemia, contrasted with the apparently rapid rise in primary gout This incorporation of glycine-N^{15} into uric acid in polycythemia vera does not follow the "metabolic-shunt" pathways, for the rate curves

are slow and consistent with the transformation of glycine to intracellular nucleic acid, then to uric acid. In two patients with secondary polycythemia they also noted delayed reduction in the glycine-N^{15} concentration of urinary uric acid in contrast to the concentration found in a patient with gout and in a control subject. This was thought to be due to overactivity of the myeloid cells in the later stage of myeloproliferation. The results of these studies verify previous opinions that in some cases of polycythemia the hyperuricemia results from overproduction of uric acid (389, 390)

In preliminary studies on polycythemia vera, leukemia and acute gouty arthritis Weissmann and associates (358) noted greater excretion of 8-hydroxy-7-methyl guanine and decreased excretion of xanthine and hypoxanthine. In Issac's discussion of patients with polycythemia and gout, he (164) mentioned a type of articular pain in both upper and lower extremities that is not accompanied by articular swelling, and possibly is associated with the increased viscosity of the blood. Erythromelalgia may occur in polycythemia, and this could be confused with acute gouty arthritis (49). Occasionally, patients with myelosclerosis experience a similar type of pain. Usually elevation of the extremity of the patient with erythromelalgia and polycythemia will afford relief from the excruciating burning sensation.

MYELOSCLEROSIS

Gout is commonly associated with myelofibrosis or agnogenic myeloid metaplasia (154, 179, 230, 378). We have seen three patients with myelosclerosis among twelve who had combined gout and blood disorders Hickling (154) pointed out that gout occurs more commonly in blood dyscrasias in which all three bone marrow elements

(granulocytic, erythroid and megakaryocytes) are involved All observers do not share his belief that such an alteration occurs more frequently in myeloid metaplasia than in polycythemia or myeloid leukemia. Hickling speculated that because gout sometimes precedes the myeloid metaplasia by many years, it may be considered the cause of the myeloid disturbance. In our three patients, symptomatic gout followed development of myelosclerosis. This was also true of the cases reported by Reifenstein (267) in which symptoms of gout developed five years after the primary diagnosis was made

Patients with gout and myelosclerosis may have the classical manifestations of gout with urate tophi and renal calculi and the gout responds favorably to routine therapeutic measures. The hyperuricemia probably results from increased erythroid and granulocytic cell activity

Laster and Muller (191) described a case of a patient with myelosclerosis in whom the first attack of gouty arthritis developed two years after splenectomy. They thought that the gout was due to more rapid turnover of nucleoproteins in conjunction with greater production and breakdown of blood cells Isotopic studies on this patient with glycine-N^{15} demonstrated a slow rate of transformation into urinary uric acid comparable to the results obtained in cases of polycythemia.

LEUKEMIA

The serum uric acid level and the uric acid miscible pool are both higher than normal in patients with leukemia, but only isolated cases of leukemia and gout are found in the literature (36, 41, 53, 111, 125, 295, 344). Possibly, some cases of polycythemia with gout represent a preleukemic stage (328) Only one of our twelve patients with gout and blood disorders had leukemia, which

was of the monocytic type, and the gout preceded the leukemia by two years. Types reported by others have been *lymphatic*, myelogenous and aleukemic Roentgenotherapy for the leukemia may be followed by the initial attack of acute gouty arthritis or gout with tophi may occur early in the course of the leukemia (216).

Forkner (111) doubted the relationship between gout and leukemia but noted a rise in the serum uric acid level after a favorable response of leukemia to roentgenotherapy, and if the serum uric acid level failed to rise, he considered the therapeutic response to be unsatisfactory. Because of the hyperuricemia that follows roentgenotherapy for leukemia, it is suggested that the smallest effective dose of roentgen ray be used and that the patients be given a low purine diet and a large fluid intake.

The white blood cell count of these patients is no different from that of others with leukemia who do not have gout. The serum uric acid levels are higher than usually seen in primary gout Colchicine will effectively control the acute gouty arthritis in these leukemic patients, and it should be used prophylactically when such patients are treated with cytotoxic chemotherapeutic agents or roentgen rays.

PERNICIOUS ANEMIA

Shortly after introduction of hepatic therapy for pernicious anemia, an association between gout and pernicious anemia was noted (287, 307). Riddle (270) noted increases in the endogenous serum uric acid and in the urinary uric acid excretion after a remission of pernicious anemia. Although administered liver extract may in itself contribute to the hyperuricemia, this is so slight that it is probably negligible The increased maturation of the red blood cells is the primary cause of the increase in en-

dogenous uric acid production and in some cases acute secondary gouty arthritis.

When pernicious anemia was treated with large amounts of liver by mouth, this exogenous supply of purines added to the woes of such a patient with gout. Hench (149) stressed the risk of precipitating attacks of gout in patients who are given liver extract. Although liver extract has been widely replaced by the more refined fractions, such as vitamin B_{12}, the risk of precipitating gout by stimulating the red cell maturation and reticulocyte activity remains Colchicine is effective for treating acute gout in these patients Avery (11) reported a peculiar case of a patient who had polycythemia that subsequently appeared to be pernicious anemia, and gout proved a problem after the polycythemia was evident

A case of non-tropical sprue (235) in which the therapeutic control with liver conflicted with satisfactory control of the gout was reported We saw a similar case of non-tropical sprue and gout in which the anemia has been adequately controlled with folic acid but the hyperuricemia has persisted Daily use of colchicine has been successful in reducing the number of acute attacks of gouty arthritis and the full toxic dose of colchicine has been sufficient to limit acute attacks to twenty-four to thirty-six hours In the case of non-tropical sprue with hyperuricemia reported by Zumoff (393), both the anemia and the elevated serum uric acid level were corrected by daily administration of 15 mg of folic acid

HEMOLYTIC ANEMIA

Some patients with hemolytic anemia have suffered from associated secondary gout (82, 107, 188, 246) Deitrick (82) pointed out that both conditions are inherited and that endogenous uric acid results from extrusion of nuclei

from normoblasts. One of his patients had symptoms o[f] gout at the age of 11 years and tophi at 14 years. Deitrick thought that splenectomy afforded relief although Lambie (188) noted no change in hyperuricemia after splenectomy in a case of juvenile gout with chronic hemolytic anemia

COOLEY'S ANEMIA

Hyperuricemia and renal calculi have been found in patients with Cooley's anemia, and in one reported case this was associated with acute podagra, which responded favorably to use of colchicine (218). We observed one patient with congenital telangiectasis (of the gastrointestinal tract) who suffered from chronic loss of blood and who had gout.

LYMPHOMAS AND MULTIPLE MYELOMATOSIS

Development of gout in patients with lymphomas is rare, although hyperuricemia and renal uric acid calculi sometimes develop in patients with lymphomas, especially after roentgenotherapy (349) or nitrogen mustard therapy (269).

There are few reports of multiple myelomatosis associated with gout (48). The articular symptoms associated with multiple myelomatosis are usually those due to nodules about the knee which represent amyloid deposits in and about these joints (323). One case of myeloma with cryoglobulinemia and gout was reported (333).

OTHER ASSOCIATED DISEASES

DIABETES MELLITUS

In 1881, Charcot (66), called attention to a report about ty years earlier by Storch of Berlin, who noted a relanship between gout and diabetes. He added that gout l diabetes are found in the same family but seldom

occur simultaneously in the same patient, and that the diabetes is not severe Garrod (122) also noted a relationship between these two diseases In 1907 Luff (209) stated, "The development of glycosuria or diabetes in persons of gouty ancestry is undoubted. . Glycosuria is generally associated with some form of irregular gout, and but seldom with the ordinary articular gout, but very occasionally it alternates with true gouty attacks, and then, while the glycosuria lasts, the patient is quite free from articular gout, and vice versa"

Until 1956 only five cases of combined gout and diabetes mellitus could be found in the English medical literature (66, 95, 165, 263). This is of particular significance since the incidence of diabetes mellitus in families of patients with gout is high. Forty-three per cent of the fifty-six patients with gouty arthritis Ishmael (165) investigated were from diabetic families, and 72 per cent had a family history of obesity Among 143 patients with gout we found abnormal blood sugar levels in forty (28 per cent), which is approximately a 50 per cent greater incidence than in a group of persons matched for age, sex and obesity. Of these forty patients only one suffered from diabetes that required insulin There was nothing clinically characteristic about these patients Similar features of gout and diabetes mellitus are: 1) the greater than normal familial incidence of diabetes in both diseases, 2) the younger the patient the worse either condition and its complications will be, 3) both maladies are worsened by stress, and 4) both are frequently associated with atherosclerosis and obesity (356)

In view of the increased family incidence of diabetes mellitus in patients with gout and the fact that many patients with gout have elevated blood sugar levels but seldom have severe diabetes, it appears that there is a

relationship between gout and diabetes and that gout or hyperuricemia alone, unlike obesity, may reduce or ameliorate the clinical manifestations of diabetes mellitus It has been noted that uric acid is diabetogenic when injected into rabbits whose glutathione level is lowered to about half the initial value by feeding a methionine and cystine deficient diet (131). It is believed that uric acid diabetes is similar to alloxan diabetes

LEAD POISONING

Older texts (129, 209) contain such statements as: "Lead gives rise to both chronic kidney disease and gout" and "Lead poisoning is held accountable for many cases of gout" (129) This condition has been referred to as saturnine gout. Lorimer (206) analyzed 107 cases of gout associated with lead poisoning. Grafe's (129) text reviewed work of other observers who noted that saturnine gout develops in one of forty patients with chronic lead poisoning and that 100 of 800 lead workers in the Harz Mountains had gout These patients with lead poisoning and gout differed from patients with primary gout in that they were reportedly younger, anemic, and had a chronic form of gouty arthritis. The vascular nephritis and diminished uric acid excretion associated with plumbism was considered to be the cause of the gout. Ludwig (207) reported two interesting cases of gout associated with lead toxicity, and he believed that the lead caused increased nucleoprotein breakdown Aub and coauthors (9) mentioned lead arthralgias involving the flexors of the knees and elbows.

Current students of gout do not see patients with saturnine gout, and only a rare case is reported Talbott (328) mentioned lead workers who were troubled with gout but had no evidence of lead intoxication In 1950,

2 cases of gout due to lead poisoning were reported by Weissenbach and associates (357). The industrial safeguards against lead poisoning are well established, and if this is a true etiologic fact in secondary gout, it is under excellent control

HYPERCHOLESTEREMIA AND HYPERLIPEMIA

Adlersberg (2) noted that approximately one-third of the families with hypercholesterolemia that he studied had hyperuricemia, but none suffered from gouty arthritis (227) One case of lipemia and gout was described in a Negro man (112)

OSTEITIS DEFORMANS

The concurrence of osteitis deformans and gout has been reported (248, 291). We have seen five patients with osteitis deformans and gout All were men ranging in age from fifty-eight to seventy years The disease involved the lumbar spine and pelvis in four of the five patients We found the incidence of osteitis deformans in 652 patients with gout seen in the Ochsner Clinic to be only 0 76 per cent whereas the incidence of gout in 164 patients with osteitis deformans was 3 per cent Three cases of osteogenesis imperfecta tarda with gout have been reported, routine therapy for gout was not fully effective (6).

MISCELLANEOUS

A case of gout and metabolic craniopathy (101) and one of pseudo-pseudohypoparathyroidism with gout (347) have been reported We have seen one case of pseudopseudohypoparathyroidism associated with gout Alkaptonuria was associated with hyperuricemia in a patient who did not have gout (193)

Older texts contain the statement that thrombophlebitis is sometimes associated with gout (209, 247) More recently Diamond (88) reported such an association in

10 of 287 patients with gout, and he believed that it occurs more frequently than by chance alone. He speculated that hyperuricemia caused the phlebitis We have seen only three of 280 patients with combined acute thrombophlebitis and acute gout, two of whom had gout associated with polycythemia vera. Except in instances in which the two conditions may be misdiagnosed postoperatively, their association is rare.

Chapter XI

TREATMENT

TREATMENT of gout and gouty arthritis must be individualized. In this respect it might be likened in part to management of the diabetic, whose diet, weight and insulin must be individually regulated Failure to evaluate the numerous factors that play a role in therapy and lack of insight into the attitude of the patient with gout may result in poor therapeutic results If gout is secondary to a blood dyscrasia, treatment of the latter is imperative For example, in a patient with hemolytic anemia and gout, successful splenectomy will not only help the blood dyscrasia but will also cure the gout (82). Use of standard treatment of patients with mild gout will result in undue inconvenience, expense and possible unnecessary risk of drug toxicity On the other hand, patients with severe gout require more than routine measures, and the usefulness of many of the drugs for severe gout depends on the correct timing of their administration, their specificity, limitations and risk of administration.

The complications of gout must be appreciated. Atrophy of muscle groups adjacent to gouty joints may be as incapacitating as acutely involved joints. Tophi may cause mechanical interference with mobility, and uric acid sludge or stones in the kidney may lead to incorrect diagnosis of renal tumors.

Since 1950, there have been gratifying and encouraging developments in the therapy of gout Improvement

in the prophylactic measures for acute gouty arthritis, discovery of newer drugs to alleviate the symptoms of acute gout and utilization of uricosuric agents in the chronic and tophaceous gouty arthritic patient have resulted in a brighter outlook for the sufferer of gout.

ACUTE ATTACK

The aim of treatment is to reduce the duration of acute gouty synovitis to a minimum, and when possible to prevent acute attacks. This necessitates recognition of the attack as early as possible and immediate institution of proper drug therapy. The patient who is susceptible to acute attacks should have available at all times an effective drug for gout, since an attack can develop at any time.

Colchicine has been the drug of choice for acute gout for many years. When given in adequate amounts at the proper time, it relieves the acute attack in more than per cent of patients.

As a rule, colchicine is best administered orally; 0.5 m or 0.6 mg tablets are given as soon as possible. Occa sionally, it is beneficial to give two tablets as the first dose followed every one or two hours by one tablet. Adminis tration of colchicine is continued until the pain is relieved, or the patient experiences abdominal cramps, nausea, vomiting or diarrhea.

Tolerance to colchicine varies greatly from person to erson. The number of tablets usually required for an ttack varies from eight to sixteen, the average being bout ten. Patients should try to determine their tolerance ose, and, if this is accompanied by unpleasant gastro- estional symptoms, reduction of the subsequent total sage by one or two tablets will still be effective with of the unwanted side effects. The hourly dosage may ve to be too rapid therapy for some patients, resulting

in gastrointestinal disturbance before an adequate quantity of the drug has been absorbed

Intermittent administration of colchicine is less effective than continuous administration Patients should be adequately instructed about the need for around-the-clock administration of colchicine, until the full course of the drug is taken Consequently, when necessary, administration of colchicine should be continued through the night. Interrupted sleep may be annoying but it is more desirable than the effects of an interrupted course of medication Sedation usually provides rest between the periods of administration

Patients should be warned that diarrhea may follow use of colchicine The necessity of administering the drug to the point of gastrointestinal toxicity has no rationale, except that experience has taught that frequently this undesirable effect must result before the acute symptoms will be relieved Laxatives or purgatives alone given to patients with acute gouty arthritis fail to alleviate articular symptoms, this indicates that this action alone is unimportant in alleviating acute gout

Paregoric, 1 dram with each watery bowel movement, will control the diarrhea Patients appreciate having this medication in case it is needed

After initial colchicinization for acute gout, use of the drug is usually withheld for twenty-four to forty-eight hours, or until gastrointestinal toxity has subsided Then, 0 5 mg or 0 6 mg tablets are prescribed once or twice daily for ten to fourteen days Such follow-up administration usually assures adequate treatment and seems to prevent recurrences that are prone to occur at that time If continuous therapy is not undertaken, use of the drug can be discontinued at the conclusion of the

follow-up period. Here again, there is need for individual management.

Colchicine tablets, in a dosage of 0.5 mg. or 0.6 mg. three or four times daily, may terminate some acute attacks of gout but in many patients it permits development of a full-blown attack that probably could have been aborted by more frequent administration of the drug.

Should an additional course of colchicine be necessary because of a recurrence, it is best to wait two or three days between courses, because if the drug is given immediately, gastrointestinal symptoms might prevent further satisfactory administration. As only 5 to 8 per cent of patients are not significantly benefited by a single course of correctly administered colchicine, this seldom presents a problem.

Colchicine may be given intravenously if oral administration is not tolerated. The usual intravenous dose of colchicine is 1.5 to 2 mg. If a single dose is not effective, the injection is repeated in four to six hours. Intravenous administration has not been used widely, although some therapists consider it to be more effective and less troublesome than oral administration. Davis and Bartfeld (81) reported a good therapeutic response without side effects from intravenous administration in fifteen of sixteen patients with acute gout, the response in the other patient was fair. These fifteen patients required two to five injections of 0.6 mg. of colchicine during a period of one to seven days. In four patients one injection aborted the attack with subsidence of pain and swelling five to fifteen minutes after the injection. Impressive beneficial results were also noted by Graham and Roberts (130).

Although gastrointestional symptoms are not as common as with oral administration, they do occur. In the series of Graham and Roberts (130), the gastrointestinal

symptoms associated with oral administration did not occur in those patients who received a single injection of 3 mg. of colchicine.

Intravenous administration may cause venous irritation Kuzell and associates (185) had five cases of severe phlebitis, some of which were symptomatic for as long as three weeks. Drug toxicities from intravenous administration have not been publicized during the past five years, but this is probably due to the fact that its current use is limited An intravenous mixture of colchicine, a salicylate and an iodide was used previously in the treatment of acute attacks of gout but because of the danger of side effects from iodine sensitivity or a salicylate reaction, this combination is best avoided.

Demecolchicine (colcemide) is one of the alkaloids isolated from the meadow saffron (colchicum autumnale) It differs structurally from colchicine in that the acetyl group at the nitrogen position is replaced by a methyl radical In animals, it appears to be considerably less toxic than colchicine It has an antimitotic effect in fibroblast cultures similar to that of colchicine Kuzell and coworkers (185) gave intravenous injections of 1 to 4 mg of demecolchicine to twenty patients with acute gout Fifteen obtained complete remission within forty-eight hours, four reported partial relief and one was not improved Eighteen of the twenty patients received only two injections The only undesirable side effect was diarrhea, which troubled two patients No local reactions were encountered similar to the phlebitis that they noted after intravenous injection of colchicine Demecolchicine, as with other cytotoxic drugs, may cause inhibition of spermatogenesis and anovulation is to be expected

Colsky and coworkers (72) reported effective treatment of acute gouty arthritis in nine of ten patients

treated with demecolchicine orally. The usual total dosage was 5 to 8 mg. in a single course of treatment and most frequently the patients received 1 mg. hourly for five to eight doses.

In our patients oral administration of demecolchicine has not been as effective as oral administration of colchicine. Several patients with moderately severe acute gouty arthritis who failed to respond to 15 mg. of demecolchicine orally improved after taking colchicine alone or with ACTH. At least 50 per cent of our eight patients receiving 5 mg. of demecolchicine three times a day failed to obtain relief. Its administration was followed by nausea and vomiting in one patient and a rash in another. Leukopenia developed in another patient after five to six months of continuous use of demecolchicine daily. This patient was given 5 mg. doses daily as a trial prophylactic agent against acute gout. The patient had numerous large tophi, some of which seemed to decrease in size during the early months of treatment, but were grossly unchanged during subsequent periods of observation. In two patients with tophaceous gout daily prophylactic doses of the drug had no apparent favorable effect on the gouty attacks. In one patient with acute gout, transient alopecia and facial depilation followed use of colcemide (354). This condition became evident fourteen days after 40 mg. of the drug had been taken during a period of eight days. The patient's scalp hair fell out freely and he did not have to shave for about ten to fourteen days, rather than daily as had been his custom previously. After two months hair on the scalp grew back and the patient resumed his daily habit of shaving. He also complained of numbness of the right hand, suggesting neuritis, and the differential blood count showed disturbed maturation of the white blood cells. A similar case of alopecia was

reported after use of only 14 mg of colcemide (232). Another patient who received 39 mg of the drug in five days had a leukemoid blood picture and alopecia, the alteration of the blood count resulted in additional confusion (166).

Phenylbutazone In 1952, the efficacy of phenylbutazone in the treatment of acute gout was reported (182, 314). This drug is considered by some (138, 174) to be as effective as colchicine. In 80 to 90 per cent of a large series of patients receiving phenylbutazone for gout the acute symptoms completely subsided or were greatly improved within forty-eight hours (185, 186). The acute pain of gout may start to subside several hours after the first dose of phenylbutazone.

For acute attacks the initial oral dose is between 200 and 400 mg, although from 400 to 800 mg is sometimes recommended. This is followed at six to eight hour intervals by 200 mg orally for four to six doses, it is then reduced to 100 mg. three or four times a day until the symptoms have subsided (363).

Seldom is it necessary for a patient to take the drug for more than five to seven days. If, after this time, the response is unsatisfactory, the diagnosis of gout should be questioned.

Phenylbutazone may be given intramuscularly for acute gouty arthritis, but in the United States the injectable material is not available on the open market. This route of administration has been more popular in the Latin American countries. The injected material can cause considerable pain locally. Rectal suppositories are also available outside the United States and some patients with gout have related to us that they are effective in relieving their acute attacks.

The fact that phenylbutazone seldom causes the acute

gastrointestinal disturbance commonly associated with colchicine makes it a desirable therapeutic agent for patients with acute gouty arthritis who suffer unduly from the gastrointestinal toxicity of colchicine. However, prolonged treatment with phenylbutazone frequently causes gastric irritation Because phenylbutazone has multiple toxic properties, some of which are significant, the dosage should be kept to a minimum, and those administering or taking the drug must be alert to untoward reactions (see under "Drugs—Phenylbutazone"). Unfortunately, even small doses of phenylbutazone have sometimes resulted in toxic reactions It has been the impression of some therapists that fewer toxic reactions occur in patients with gout who use phenylbutazone than in other patients who take the drug for some other malady. The relatively low reported incidence of toxicity in patients with gout treated with phenylbutazone may be due to the fact that most patients with gout are males, who seem less susceptible to side reactions of the drug than females (males 27 to 29 per cent; females 43 to 47 per cent); and also because the course of therapy is usually less than ten days.

Phenylbutazone appears to be compatible with use of other drugs, such as colchicine, ACTH, probenecid, narcotics or analgesics, which the patient with gout may need. If given for any period of time to patients with congestive heart failure, the free use of sodium or administration of an alkalizing agent containing soda must be avoided. Because phenylbutazone is no more effective than colchicine, it is advisable to prescribe it only for patients who fail to respond favorably to colchicine.

Hormones. When administered in adequate amounts ACTH provides relief of acute attacks of gout in 90 per cent of patients. Pain may disappear within a few hours

and swelling and redness subside by the end of the second day of therapy.

Corticotrophin (ACTH) gel is given in doses of 40 to 80 units intramuscularly, and the aqueous preparation (20 units) is given intravenously every four to twelve hours Injections of corticotrophin gel can be repeated at intervals of eight to twelve hours for two to three days Also, intravenous administration of aqueous ACTH can be continued for an equally long period. We have never had to administer ACTH longer than three days for complete relief of an acute attack Usually by the time the patient has received 100 to 120 units of corticotrophin gel or two infusions of 20 units of ACTH, the acute gouty symptoms have abated

It is the consensus that ACTH is not as effective as colchicine in the management of acute attacks of gout. Therefore, corticotrophin gel should be tried only if the acute attack does not respond favorably to other drugs or if full doses of colchicine prove too toxic We have found ACTH to be helpful in patients suffering from long, drawn-out, acute or subacute attacks of gout that will not completely subside with colchicine Hospitalization of these patients and treatment with ACTH and colchicine will frequently result in reversal of the process The major indication for ACTH is refractoriness to colchicine

It is imperative that the patient be given colchicine during and after administration of ACTH (138, 241, 375) Otherwise, rebound attacks of gout may occur one or two days after withdrawal of ACTH therapy Administration of ACTH to a patient with gout during a quiescent period may be followed in several days by an acute attack of gouty arthritis.

It is usually not necessary to give a toxic dose of colchicine at this time Oral administration of 0 6 mg. of

colchicine one or three times daily during administratio of ACTH, and for seven to ten days after its discontinu ance, will prevent a flare-up due to corticotrophin withdrawal The daily dose of colchicine again must be individualized, for if 0.6 mg. three times daily causes diarrhea, its use should be discontinued for twenty-four hours and then restarted with the same dose twice daily. If colchicine cannot be taken orally, phenylbutazone (0 6 mg three times a day) may be prescribed for a similar period Since combination of ACTH and phenylbutazone may increase the risk of fluid retention, added precautions along this line will be needed

Cortisone in doses of 200 mg. or more daily may alleviate the symptoms of acute gout, but therapeutic failures with this steroid are frequent (115, 325) and occasionally patient's symptoms are aggravated after taking the medication. Withdrawal recurrence also occurs with cortisone and necessitates similar precautions. Other corticoids have not been spectacularly helpful for patients we have treated for gout. Further evaluation of the newer analogues as they appear may be useful. Cortisone and its allied drugs should be used for acute gout only after the more conventional specific agents have proved to be ineffective after adequate trial.

Intra-articular injection of hydrocortisone or prednisolone has been helpful in terminating an acute attack of gout (157, 351). The temporary discomfort the injection may cause is usually worth the relief that follows. Injection of 25 to 50 mg. of hydrocortisone acetate or hydrocortisone tertiary butyl acetate, or 10 to 20 mg of prednisolone into an acute gouty joint provides relief of pain within a few minutes or several hours. Usually one injection will suffice but occasionally two injections may be

required. It is likely that additional medications of this type will be developed.

Colchicine or phenylbutazone should be given daily as prescribed for the patient receiving ACTH for acute gout.

Intra-articular injections of hydrocortisone or its analogues should be given only to selected patients with acute gout or after the more commonly used drugs have failed to provide relief. We have found this method of treatment helpful in patients with gastric lesions, such as a bleeding ulcer, which prevent or make it too risky to use toxic doses of colchicine or large amounts of ACTH. When acute gout is resistant to conventional methods and located in an osteoarthritic joint, intra-articular injections of hydrocortisone may be quite helpful.

Aspirin or Salicylates. Acute gouty arthritis, characterized by mild or, at most, moderately severe pain, may occasionally be relieved by large doses of aspirin or salicylates. Usually, patients with significantly painful acute gouty arthritis or those who have more than a rare attack will find aspirin and salicylates insufficient for relief (66). Despite this, patients can be advised that, if they experience an acute attack of gouty arthritis and do not have the necessary drugs, such as colchicine, aspirin may be taken in large doses. Salicylates can also be used in conjunction with colchicine or ACTH in the treatment of acute gouty arthritis.

Narcotics. Routine control of the pain of acute gouty arthritis with narcotics is not recommended. Occasionally, however, relief of severe pain is necessary before specific agents become effective. The smallest effective dose of narcotic should be used. Hypodermic injections of codeine, Demerol * or morphine are usually helpful in such patients.

Ancillary Procedures. The extremely painful joints patients with acute gout can be protected by a crad foot boards or soft dressings. Splinting such joints w probably be unsuccessful.

Weight bearing on involved joints should be avoided If necessary, a cane or crutches can be used. An arm sling may permit continued mobilization in a patient with involvement of one or more joints of the upper extremity.

Hot or cold applications to the painful joint must be used with caution. Sometimes application of heat will increase the pain. Cold packs early in an acute attack may provide some relief.

Articular effusion may be so extensive that aspiration is indicated and this is particularly true of the knee joint. The joint should not be aspirated immediately upon onset of the attack nor should colchicine therapy be withheld until the articular fluid can be completely studied Usually, the slightest manipulation of the joint causes considerable discomfort Specific drug therapy should be initiated so that the patient is afforded some relief before physical measures are given too much attention Sometimes it is only after subsidence of the associated edema surrounding the joint that the degree of articular effusion can be correctly estimated. Seldom is it necessary to aspirate the joint more than once. If the joint is not too sensitive, an elastic pressure bandage may be applied after aspiration. Fluid intake should be maintained at a high level, as dehydration increases the possibility of development of renal stones.

Diet. The diet of a patient suffering from acute gouty arthritis is frequently controlled by the patient's desire for food, and alteration of that desire by drugs that are administered at the time. During an acute attack a liquid or bland diet in moderation is most desirable. A low

purine, low fat, high carbohydrate soft diet is recommended by most therapists Such a diet is enthusiastically accepted by patients experiencing the severe pain of acute gout (see Diet Section). Fluids should be encouraged All alcohol should be avoided during the acute attack

INTERVAL PHASE

The intervals between acute attacks of gouty arthritis vary in duration so much that a program of therapy must be tailor-made for each patient At such times the patient is usually asymptomatic, active, with or without hyperuricemia, and frequently disinterested in any inconveniences or treatment. The less severe the previous attack of gout, the longer the interval between attacks, and the infrequency of attacks of acute gout all lessen the patient's enthusiasm for an active program of treatment during the interval.

The interval period between attacks can be divided into three different phases, and treatment varies accordingly. One phase is characterized by only a few acute attacks (less than four during a period of about five years) which have responded promptly to treatment and have left no residual. Another phase is characterized by four or more acute attacks in a similar period, with greater periods of incapacitation, and shorter intervals of relief between attacks A third phase is characterized by residual articular damage or deformities of chronic gouty arthritis

These different intervals between exacerbations of acute gouty arthritis require continuous therapy, but this should be selective and individualized The types of therapy needed in the interval phase appear rigid and possibly academic but offer a working plan for most patients with gout. Possibly a simpler rule would merely call for the

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INTERVAL PHASE

The intervals between acute attacks of gouty arthritis vary in duration so much that a program of therapy must be tailor-made for each patient At such times the patient is usually asymptomatic, active, with or without hyperuricemia, and frequently disinterested in any inconveniences or treatment. The less severe the previous attack of gout, the longer the interval between attacks, and the infrequency of attacks of acute gout all lessen the patient's enthusiasm for an active program of treatment during the interval.

The interval period between attacks can be divided into three different phases, and treatment varies accordingly One phase is characterized by only a few acute attacks (less than four during a period of about five years) which have responded promptly to treatment and have left no residual Another phase is characterized by four or more acute attacks in a similar period, with greater periods of incapacitation, and shorter intervals of relief between attacks A third phase is characterized by residual articular damage or deformities of chronic gouty arthritis

These different intervals between exacerbations of acute gouty arthritis require continuous therapy, but this should be selective and individualized The types of therapy needed in the interval phase appear rigid and possibly academic but offer a working plan for most patients with gout. Possibly a simpler rule would merely call for the

complete treatment for every patient, and especially continuous uricosuric therapy with all recurring attacks of gout (23).

In great part the patient's attitude and understanding will determine the success of therapy. It is usually impractical for a patient who has had only one attack of acute gouty arthritis that responded promptly and completely to therapy to follow a strict diet and to take drugs daily for the rest of his life. However, some therapists believe that at these times patients need to be treated vigorously, with all possible agents and strict dieting

Because most patients who have had one attack of acute gouty arthritis will eventually suffer additional attacks, and because crippling arthritis may ensue in anyone with gout, we suggest an active but selective practical approach to the treatment of interval gout. Again, like diabetes, the severity of the condition determines the extent of therapy.

A modified program is advocated for the patient who has had less than four attacks of acute gout in five years and whose attacks have caused incapacitation for less than two weeks and left no residual articular damage. If the patient's weight is normal, such a program is based on a qualitative diet and drugs. A diet devoid of an excess of fat and purine is recommended, although it is realized that the endogenous source of purine is always present and some observers consider the dietary intake of no importance. However, it appears unreasonable to add purines to a metabolic pool that may already contain an excess amount of uric acid. We recommend a diet in which the items listed in Food Omitted, Stage II (Diet Section) are deleted Obesity, when present, should be corrected by use of a low purine, low fat reduction diet. Too rapid loss of weight should be avoided. Many pa-

tients experience attacks of acute gouty arthritis when they lose weight too rapidly This is discouraging to such patients and causes dissatisfaction with dieting If no more than ½ to ¾ lb is lost weekly, acute attacks of gouty arthritis may be avoided. If the patient needs to lose a considerable amount, or he has a history of flare-ups of acute gouty arthritis with loss of weight, it is advisable to administer 0 6 mg of colchicine daily to prevent attacks of acute gouty arthritis

A low purine, low fat diet composed of Foods Allowed, Stage II (Diet Section) is recommended for all patients with a diagnosis of gout The diet should be well balanced and contain sufficient protein to fill the daily metabolic need Fermented beverages, such as wine and beer, are best avoided Distilled liquors should be used in moderation

Colchicine may be prescribed daily during the interval phase of gout It is recommended that 0 6 mg be used daily after an attack of acute gouty arthritis For patients who have had an initial attack, it need be continued only two or three weeks in order to avoid any flare-up of gout during what seems to be a susceptible period For patients who have had more than one but less than four attacks of brief duration during a period of five years, this same brief follow-up treatment with colchicine can be prescribed after each acute attack More frequent attacks of acute gouty arthritis warrant daily administration of colchicine as prophylaxis against acute gouty attacks. A group of our patients with gout who were treated during the interval phase with low fat, low purine diet plus daily administration of colchicine showed fewer attacks and less severe gouty arthritis in 50 per cent of cases observed during a period of several years No toxic reactions were noted. Colchicine 0 6 mg. was prescribed once or twice

daily for these patients. Continuous use of colchicine during the interval phase is recommended (139, 202)

The patient who has suffered more than four attacks of acute gouty arthritis, who is incapacitated after subsidence of the acute attack, whose attacks are increasing in frequency, or who has uric acid tophi should be placed on a full program of therapy in the interval period. These patients should avoid an excessive amount of exogenous dietary purine, and should have the meals prepared from the items listed in Stage II Diet.

Colchicine. Daily administration of colchicine in doses of 0 5 mg or 0.6 mg. is recommended Many variations of this schedule have been used, such as use of colchicine five out of seven days each week. Should a gastrointestinal upset or diarrhea occur, use of the drug can be discontinued for a few days until these symptoms subside, after which use can be resumed. Colchicine should be administered to the gouty patient who is losing weight as a result of dieting.

Probenecid has been established as a satisfactory uricosuric agent for patients with gout. Its mode of action is discussed on page

Hyperuricemia can often be corrected or lowered by daily administration of probenecid in both the interval and acute phases of gout. However, the drug does not relieve the pain or inflammation associated with acute attacks (251). Administration of probenecid precipitates acute attacks during the first several months of its use in about 10 per cent of patients but this can sometimes be prevented or partially controlled by simultaneous daily use of colchicine in doses of 0 5 mg or 0.6 mg (138, 323).

The problem in prescribing probenecid is when should the patient start taking the drug? The diagnosis of gout signifies disturbed purine metabolism, hyperuricemia and

arthritis. Ideally, all measures to correct these should be instituted when the diagnosis is made. However, when such a drug is prescribed, it must be administered with the knowledge that current information indicates it will be needed daily for the remainder of the patient's life If probenecid is indicated today, the metabolic defect it influences will probably be as profound in later life It should be understood that not all patients with gout have progressive disease Approximately one out of four of our 280 patients had had less than four attacks, which leads us to believe that prescribing probenecid for *all* patients with gout is not really necessary Smyth and coworkers (303) noted that "Unless the patient has reached that stage of the disease when he becomes concerned about its crippling potentialities, he is not likely to adhere to the regimen of daily probenecid therapy" We agree with their recommendation that probenecid be given to patients who experience three to four attacks a year and are sufficiently concerned to accept a program of continuous drug therapy

Probenecid should be administered to all patients with chronic gouty arthritis and to other patients who have more than two attacks of acute gouty arthritis yearly in successive years, or yearly attacks that cause incapacitation for more than two weeks and occur in patients with persistent uric acid content above 7 mg per cent It is also indicated in patients in whom the frequency of attacks of gout and duration of incapacitation of joints increase steadily during a period of four to five years The presence of visible tophi is considered an indication for administration of probenecid Usually patients with these lesions experience attacks of acute gouty arthritis sufficiently often to warrant use of the drug The younger

the patient with such a pattern of gout, the stronger the need for an adequate uricosuric agent.

The oral dose of probenecid is 0.5 Gm. A daily dosage of 1.5 Gm. is effective in 75 to 80 per cent of patients. In the treatment of chronic gout with probenecid, Gutman and Yu (139) noted that 25 per cent of the patients needed, every twenty-four hours, 1.5 to 2 Gm., 50 per cent required 1.0 Gm., only 10 per cent needed 0.5 Gm. and 15 per cent had to take 2.5 to 3 Gm. for effective therapy. The dosage should be determined by the serum uric acid level, which should be maintained below 5.5 mg./100 ml (202). The usual initial dosage is 0.5 Gm. once daily. If no untoward reaction occurs, the dosage is increased to 0.5 Gm. twice daily or three times daily. Probenecid should be administered continually once the decision has been reached that a uricosuric agent is indicated, for drug sensitization is more likely to occur if given intermittently. As more effective uricosuric agents are developed and prove to be safe, undoubtedly they will be substituted for probenecid. The indications and cautions for use of these drugs are similar.

Colchicine should be prescribed daily during the first few months of probenecid therapy and indefinitely if recurrent acute gouty arthritis persists, for it appears that during the first nine months of probenecid therapy the patient's liability to acute attacks of gout is increased.

The patient should drink sufficient water to insure daily urinary excretion of 2000 cc. or more, since probenecid increases the chances of formation of uric acid gravel and genito-urinary symptoms, such as renal colic (42). Alkalinization may prevent formation of uric acid gravel and crystals, and it could be beneficial during the first weeks of probenecid therapy when uricosuria is increased.

Some authors (23) recommend, in addition to increas-

ing the daily fluid intake to 2 to 3 liters during the initial weeks of probenecid therapy, that the patient use a hydrometer to determine if the specific gravity of the urine rises above 1 010, which would be an indication for more fluids Nitrazine paper can be used to check the pH of the urine This can be done by the patient several times daily. The urine should be kept at a pH of 7 or above 6 Normotensive patients can be given sodium citrate for alkalinization of the urine and hypertensive patients can use potassium citrate Management of renal uric acid stones in these patients is discussed on page

If an acute attack of gout occurs during probenecid therapy, use of the drug should be continued and treatment for acute gouty arthritis should be initiated For this purpose colchicine, phenylbutazone or steroids can be used Salicylates are contraindicated, as they may be mutually inhibitory in their action on tubal excretion (136) A uricosuric agent in secondary gout has been advocated by some only in patients with disabling chronic articular disease because of the additional risk of ureteral obstruction by uric acid crystals (23)

Phenylbutazone is also effective in controlling the symptoms of chronic gouty arthritis, as well as in decreasing the frequency and severity of acute gouty arthritis (303) Kuzell and coauthors (187) noted prophylaxis of acute exacerbations of gout and relief of the discomfort of chronic gouty arthritis with small doses of phenylbutazone Smyth and associates (303) found that 300 to 600 mg of phenylbutazone daily was necessary for this effect, but the serum urate level was not always reduced It is now generally agreed that moderately large doses of phenylbutazone are necessary for uricosuric action For this reason, the drug should not be given continually for

gout. Also, prolonged use of large doses may cause toxic reactions, which can be of major consequences.

In selected cases of gout, not controlled by routine measures, in patients with severe acute attacks, or in those requiring relief from the discomfort of chronic gouty arthritis, continuous daily use of phenylbutazone for a long time may be considered. The lowest possible daily dose of phenylbutazone should be prescribed and all possible precautions taken to prevent toxicity. Simultaneous administration of other drugs is to be avoided.

Salicylates. Continuous prolonged administration of salicylates in the interval phase of gout fulfills several aims of treatment (93). Salicylates have a uricosuric effect similar to that of probenecid. They also often control the pain of chronic gouty arthritis, and in the opinion of some observers (224, 386), protect the patient from further acute attacks.

The uricosuric properties of salicylates were observed long before probenecid became popular for this effect (99, 209) It was known that the serum uric acid level could be reduced 30 to 50 per cent by daily administration of salicylates, but it was generally believed that this effect was limited and ineffective during a long period of time (22, 223) or that salicylism prevented adequate dosage (134, 324) The uricosuric effect of salicylates was verified more recently by Marson (223) and Yu and Gutman (386), who had patients whose tophi were reduced in size and showed progressive radiologic improvement after continuous prolonged administration of salicylates

Salicylates must be given in daily doses of 5 to 6 Gm to be effective as a uricosuric agent (22, 386). Lesser amounts may cause uric acid retention. The drug must also be given for long periods. Because many patients

cannot tolerate large doses of salicylates, the usefulness of this drug is limited. Marson (222) was able to maintain his patients on large doses of salicylates, and noted that although salicylism developed initially, in many patients tolerance was acquired within one to six weeks.

As a uricosuric agent, salicylates are cheaper than probenecid and do not precipitate acute attacks of gout when first administered. In some patients with gout and renal disease drug-induced uricosuria is less pronounced than in those who have no renal disease. In the former group reduction of glomerular filtration diminishes the quantity of water available for tubular reabsorption. It has been suggested that these patients have a greater uricosuric response to large doses of salicylates than to probenecid (70).

The analgesic and antirheumatic properties of salicylates make it effective in relieving some of the pain of chronic gouty arthritis (22). Bauer and Klemperer (22) did not think it was possible to prevent acute attacks of gout by administration of salicylates. In our limited observation continuous administration of salicylates does seem to reduce the frequency of acute attacks. If tolerated in adequate amounts, they may prove beneficial for interval therapy in limited cases. Because of the uricosuric property when given in large doses, adequate precautions should be taken to prevent formation of urinary uric acid stones or sludge (See under probenecid).

Steroids. Continuous administration of steroids or ACTH for therapy of the interval phase of gout is not recommended routinely. However, there is a report (7) of a patient who took 50 mg of cortisone daily for twenty-two months, during which time only a few mild attacks of acute gout occurred in contrast to the preceding period when he suffered frequent severe acute attacks. More-

over, nodules assumed to be tophi gradually became smaller and then completely disappeared. The serum uric level remained unchanged, being between 7 and 10 mg per 100 ml.

If all other measures fail to afford relief, steroids could be tried. The untoward reactions of these drugs make their prolonged use unwise, and if circumstances necessitate interrupted therapy, attacks of gout may follow their withdrawal *If given, the smallest effective dose should* be prescribed,

Extraneous Factors. It is wise for the patient with gout to be aware that during the interval phase an attack of gout may be precipitated by trauma or excesses, especially of food and drink. Adequate rest is imperative and physical overexertion during holidays and trips must be avoided. Emotional disturbances seem to precipitate an attack in some patients Dehydration should be avoided During holidays, trips and festive occasions, in some patients the dosage of colchicine may have to be increased to 0 6 mg twice or three times a day rather than once daily.

CHRONIC GOUT

The therapeutic program in chronic gouty arthritis consists of treatment of both the acute attack and the interval phase Acute attacks occur during the chronic phase and these require active treatment with colchicine, phenylbutazone, or ACTH, as previously discussed. Medical supervision of an acute attack is advisable because frequently this stage of the disease may represent a previously neglectful attitude or discouragement in a crippled gouty arthritic. It is always important to prevent or shorten all attacks of acute gouty arthritis

In the chronic stage a low-purine, low-fat, moderately

high-carbohydrate diet (Stage I Diet) should be well established Obesity, if present, needs correction and the dietary precautions discussed under this heading and the treatment of the interval phase of gout should be observed.

Physical therapy in the form of local applications of heat, hydrotherapy and exercises may be helpful Occupational therapy is of value in discouraged patients who can no longer carry on routine manipulations with their hands With acute gouty arthritis that lasts unduly long or with chronic involvement the muscles associated with a large involved joint may be atrophied and inadequate for support Flexion deformities in the knees may result if these joints are propped up with pillows or held flexed for long periods of time when the patient is bedridden Correction of these mechanical defects and rebuilding of the adjoining musculature are necessary to secure a stable, comfortable joint in some patients with chronic gouty arthritis In such patients crippling is due to the atrophy of muscles rather than to the gout itself

Probenecid is recommended for all patients with chronic gout who have adequate renal function If the kidneys are significantly damaged or have considerably reduced function, probenecid should be prescribed only with full appreciation of its action Large doses of salicylates may be preferable. Additional urate deposits may develop in the kidney of these patients if they take probenecid, but if the stage of therapy could be reached in which the excessive urate deposits in the kidneys are then removed from the interstitial tissue, this drug would prove helpful

If probenecid is not administered, salicylates may be used as a uricosuric as well as analgesic agent When used for these reasons, the action of the drug and pre-

cautions discussed in the drugs for the interval phase of gout must be known to the therapist.

In the chronic stage of gout, tophi may interfere with normal function of the joint or wearing a shoe. This may be due in part to ulceration of the skin, overlying the tophi Such tophi can be removed surgically with good results These incisions heal satisfactorily and rarely do tophi of significant size recur at the site of former removal. Surgical removal of large tophi can be relatively simple but it may also be most difficult. Not all urate deposits in and about joints and tendons in far advanced cases of gout are well demarcated, and they may tend to extend into the adjoining tissues or surround nerves and blood vessels so that meticulous surgical dissection is required. Preservation of the blood supply, especially in tophaceous fingers and toes, may be challenging to the operator.

Daily imbibition of large quantities of water is important for patients with chronic gouty arthritis. If they have a history of renal stones, alkalinization of the urine, as discussed in therapy of the interval phase of gout, should be considered.

Patients with chronic gout must be particularly careful to avoid stress. Operative procedures should be undertaken with added precautions for exacerbations of acute attacks Adequate rest and mental, physical and emotional well being are necessary for the continuing quiescence of gout in these patients.

Preoperative Management. Because patients who have had acute gouty arthritis frequently have an acute attack after an operation, it is important to treat patients prophylactically in an effort to prevent such recurrences This is even more important if the gout is progressive, is difficult to control, or lasts for long periods In such patients it seems logical to advise low-purine, low-fat, high-carbo-

hydrate diet (Stage II) for one week before operation Colchicine, 0 6 mg. twice daily for five to seven days preoperatively, should be administered to these patients if possible. Postoperatively, if colchicine can be taken orally, its administration, once or twice daily, should be started as soon as possible Intravenous administration of colchicine is indicated when the patient is unable to take the drug orally The average intravenous dosage of colchicine is 1 mg to 1 5 mg daily When possible, even patients with less severe gout should be given colchicine preoperatively and postoperatively, for it is impossible to predict in which patient acute gouty arthritis will develop Bartels (16) suggested that for the surgical patient with gout who cannot take oral medication, relief may be obtained by cutaneous administration of 500 ml of a 20 per cent solution of glucose twice daily

SECONDARY GOUT

Secondary gout may exist as a complication of some other disease, usually one involving the hematopoetic system Primary and secondary polycythemia (339, 342, 388), chronic leukemia (41), Cooley's anemia (218), myelosclerosis (154, 191), pernicious anemia, chronic hemolytic anemia in adults, and the malignant lymphomas may precede and then be complicated by gout This is the result of an increase in the breakdown of nucleic acids, and then release of intermediary purine and uric acid into the blood stream

In these patients the primary disease must be treated as well as the gout. Surgical correction of a congenital cardiac defect causing secondary polycythemia resulting in gout will correct both complications Successful splenectomy, which alleviates hemolytic anemia that has precipitated gout, will also eliminate the gout Control of

pernicious anemia with vitamin B_{12} will eventually control the gout it has caused In these patients the therapy may also precipitate acute gouty arthritis, but with modern vitamin B_{12} treatment, fewer such provocative attacks are to be expected than when frequent injections of liver extract were needed for adequate treatment of the anemia.

Control of some of the secondary causes of gout makes

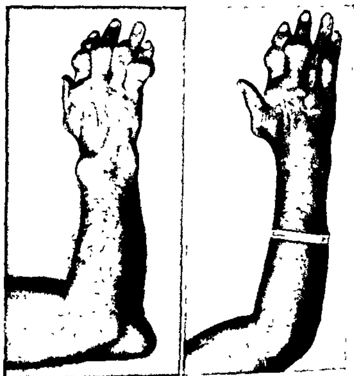


Fig. 53: A Arm of patient with gout of twenty years' duration
B Tophectomy improved mobility of extremity

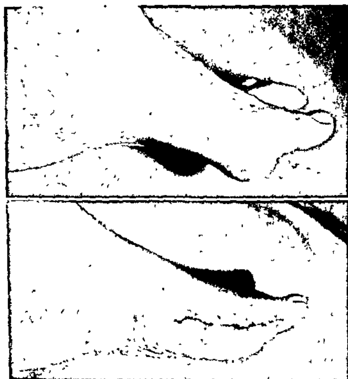


Fig 53 C. Foot of patient with gout of twelve years' duration D Tophectomy permitted wearing of regular shoes with comfort

this type of gout reversible. Unfortunately, these cases are rare

Treatments of attacks of secondary acute gouty arthritis or complicating chronic gouty arthritis is the same as for primary gout Caution has been sounded (135) and endorsed (23) that active treatment of the primary hema-

tologic disease that is giving rise to secondary gout may result in an additional plethora of nucleic acid end products and uric acid into the blood with overloading of the renal excretory mechanism. The concomitant use of uricosuric agents in these patients necessitates additional caution and understanding of the problem.

SURGICAL TREATMENT

Surgical treatment of gouty joints and extra-articular tophi is sometimes beneficial to patients with gout. Troublesome tophi can often be removed satisfactorily. This may facilitate wearing of shoes, use of the hands, or movement of the part (Fig. 53). It may also be desirable to remove a tophus for cosmetic reasons. Widespread tophi of the fingers that are ulcerated and draining (189, 199) may be improved to some degree by extensive surgical removal of urate deposits and granulomas in and about joints. Such cases must be selected carefully, however. Damage to the vascular and nerve supply of the fingers must be avoided, and every effort must be made to preserve function of the joint. Successful surgical removal of a surface tophus can prove difficult, for urate deposits may extend root-like into underlying tendons, muscles, and nerves, and around blood vessels (Fig. 54). These extensions require curettage and careful removal, and this may prolong what appears to be a simple, brief surgical procedure into an operation of several hours' duration. Failure to remove the tophaceous material located deeply beneath the operative site will often give a poor postoperative result.

A general anesthetic will frequently be needed for operation on the deeper extensions of urate, whereas regional nerve blocks may prove adequate for surgical removal of smaller deposits. It is unwise to plan use of



Fig. 54. Surgical exposure of the left first metatarsophalangeal joint of a man who had had gout for twenty years The uric acid deposits are diffusely scattered in and about the joint so that surgical removal of all the deposits is difficult

only a local anesthetic for adequate removal of tophi, which may have subcutaneous extensions of urates

Surgical removal of large extra-articular deposits of uric acid will reduce the total body uric acid content and probably make the modern uricosuric agents more effective in reducing surgically inaccessible urate deposits in other parts of the body Use of uricosuric agents will undoubtedly reduce the number of damaged bones and joints of gouty patients, and thereby curtail the need for amputation of such parts, which become functionless or persistently painful

Removal of digits because of irreparable gouty damage is still necessary at times When a digit is removed because of urate deposits, the line of amputation should

be free from any significant gouty involvement. Surgical removal of other sites, such as the patella, involved with gouty changes, may also prove beneficial after other indicated measures have been ineffective (Fig 55a). Larmon and Hurtz (189) reported successful replacement of the femoral head with an intramedullary type prosthesis in a patient with gouty destruction of the hip joint.

Fortunately, the incidence of infection after surgical treatment of a tophus or gouty lesion is almost nil. Routine prophylactic administration of penicillin to these patients is unwise, for it may precipitate an acute attack of gout.

Kersley and associates (173) noted that in three of six patients whose gout was associated with anemia, which was probably acholuric jaundice, splenectomy benefited the gout

Adequate prophylactic administration of colchicine (1 5 mg./day) for at least five to seven days preoperatively and ten to twenty days postoperatively is essential to keep acute postsurgical gouty arthritis to a minimum. Intravenous administration of colchicine should be used if oral administration is not feasible. A low purine, low fat intake before and after operation is also indicated

URIC ACID NEPHROPATHY AND URIC ACID LITHIASIS

Hyperuricemia may result in formation of uric acid stones, deposition of uric acid in the renal tissue, or both Hench (152) reviewed a report of two of three patients with gout on whom necropsy was done who had urate deposits in the renal tubules. Hyperuricemia is usually associated with primary or secondary gout. In secondary gout elevated serum uric acid with complicating renal changes may occur before as well as after treatment of the blood



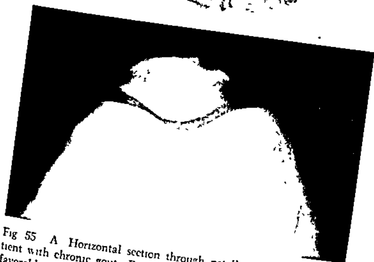


Fig 55 A Horizontal section through patella removed from patient with chronic gout Pain referable to patella did not respond favorably to conventional therapy Degenerative changes are seen on posterior surface of patella and gouty changes anteriorly B Roentgenogram of knee showing defect in patella described in A

dyscrasia. Radiologic or cytotoxic treatment of the lymphomas is probably the most common cause for development of acute renal failure due to uric acid crystallization in the kidney. This results from sudden release of large amounts of endogenous uric acid with hyperuricemia (126), uricosuria and urinary obstruction by uric acid crystals and urates (54). Weisberger and Persky (349) noted that in 283 patients hospitalized for various types of lymphomas the incidence of renal calculi was 5.3 per cent, compared with 100 patients with other metastatic malignant lesions but no calculi, who were treated by irradiation. This complication is more easily appreciated when one considers the observations of Sandberg and associates (280), who found that in untreated acute lymphocytic leukemia the mean value of uric acid excretion in the urine was 30.3 mg./kg. of body weight/24 hr. and in untreated acute myelocytic leukemia, chronic myelocytic and chronic lymphocytic leukemia, uric acid excretion was less than 14 mg./kg./24 hr. compared with 6.5 mg./kg. of body weight/24 hr. for normals.

The physician who treats patients with lymphomas who have renal impairment or renal stones must have an understanding of the complications of therapy (269). Some of these patients may have ureteral obstruction due to enlarged lymphomatous structures along the ureters, lymphomatous infiltration in the kidney or complicating pyelonephritis.

Because the therapeutic and cellular destructive response of tissue to roentgenotherapy and cytotoxic agents varies from patient to patient, it is impossible to determine the exact safeguards for preventing uremia due to obstruction of the kidneys with uric acid crystals or formation of uric acid calculi. It is therefore advisable to avoid use of more than the average dosage of any agent

with cell-destroying properties in patients with lymphomas. If renal impairment be evident before therapy of the lymphoma is begun, the risk of uremic complications is, of course, even greater

If possible, the minimal effective dose should be used in the treatment of lymphomas or multiple doses should be employed (nitrogen mustard should be injected in divided doses rather than one large dose) These patients should be kept on a low-purine, low-fat diet with adequate calories to prevent nutritional deficiencies. Their urinary output must be at least 2000 cc daily, and the urine should be kept alkaline Uricosuric agents, such as probenecid or large amounts of salicylates, should be avoided at these times

Pyelonephritis should be treated with the proper chemotherapeutic agents, sufficiently long to eliminate the bacterial infection in the kidney If the kidney is the site of lymphomatous infiltration, local roentgenotherapy of the kidneys first may be helpful in preventing subsequent obstruction Ureteral obstruction by urate or uric acid sludge or stones will require cystoscopy, skillful manipulation of ureteral catheters and possibly irrigation to relieve the obstruction and uremia

Before any type of therapy, thorough renal function studies should be done. In some patients with lymphoma who receive irradiation or cytotoxic agents, the blood urea nitrogen level may rise, within twenty-four to forty-eight hours, from normal to above 100 mg per 100 cc

The incidence of renal stones in patients with primary gout is about 15 per cent Passage of a uric acid renal calculus may be the first clinical manifestation of a gouty metabolic alteration, and this occurs in about 3 per cent of patients who subsequently experience gouty arthritis Uric acid stones probably develop because of uricosuria,

and failure of continued solubility of uric acid is due to acidified or concentrated urine. Uratosis may occur in the interstitial tissue about the collecting tubules, and if near the surface of the renal pyramid, may be extruded with some of the associated granuloma and form the nidus of a renal calculus. There is evidence that some uric acid renal stones may be due to an indirect result of an acquired isolated defect in renal tubular secretion. Such patients with idiopathic uric acid stones have been found to have hypocalciuria and very acid urine (153a).

Therapy for renal lithiasis associated with urarthritis is both preventive and direct. Although the source of endogenous uric acid cannot be controlled in these patients, this is not believed to negate the need for reducing excessive exogenous or dietary uric acid precursors. Patients who are prone to formation of uric acid stones should use a low-purine, low-fat diet (Stage II) as recommended on page . It is imperative that these patients excrete at least 2000 cc. of urine daily and that, if possible, the urine be alkalinized

Probenecid will cause increased urinary output of uric acid, and during the initial period of its administration renal colic with passage of uric acid sludge or small calculi may occur Uricosuric agents, such as probenecid or large doses of salicylates, are not contraindicated in a patient with gouty lithiasis for, if effective, the uric acid deposits in the renal tissue may be reduced. In this way the granulomatous reaction in the kidney is reduced and renal function is improved. The first sign of the nephropathy of gout is considered by some to be an indication for a uricosuric agent (104) Bernstein and associates (32) reported prompt reduction in the number and frequency of occurrence of renal uric acid stones in a hyperuricemic patient who did not have gout after treatment

with probenecid, after treatment for twenty-nine months stones stopped forming. If uricosuric drugs are administered to patients with a history of uric acid renal stones, it is imperative that the precautions previously outlined be observed.

The urologist should be consulted about all patients with gout and renal lithiasis, for, whereas surgical removal of these stones is necessary in less than 15 per cent of patients, irrigation of uric acid sludge from the renal pelvis or manipulation or crushing of stones along the urinary tract may be vital in management of the patient and preservation of adequate renal function.

The composition of all renal stones should be determined, since some calcium stones may have a uric acid nidus. Too energetic alkalinization of the urine may hasten formation of calcium stones.

The surgical removal of uric acid stones differs in no way from operation for other types of renal calculi.

Pyelonephritis is frequently associated with renal calculi. Every effort should be made to identify the causative organism. An effective drug must be used long enough and in sufficiently large doses to eliminate the bacterial infection. Inadequate amounts that fail to eliminate the pyogenic infection in the renal tissue will mask further damage, and eventually renal function will be further compromised as the infection spreads.

Adequate Urinary Output. Instructing a patient to drink more water or even a fixed amount daily does not always accomplish the desired result. Patients' fluid needs vary greatly. It is more satisfactory if such patients are told to drink sufficient water until the minimum daily urinary output is 2000 cc by measurement. The patient can measure his urinary output on weekends or holidays and in this way determine his fluid needs. Another means

of maintaining adequate urinary output and a safe measure of solubility of the urine is to have *the patient test* his urine each morning and evening with a hydrometer and try to drink enough fluids to keep the specific gravity of the urine at 1.010 or below. A patient can be taught to do this with little effort or expense. As many hydrometers are inaccurate, the patient's instrument should be checked

Adequate fluid intake is important for all patients with hyperuricemia, and this phase of therapy should be strongly encouraged and frequently reviewed with the patient These extra fluids provide added solvent for urates and uric acid.

Alkalinization of the Urine. *Alkalinization of the urine* of the patient with gout and renal stones may be difficult and challenging. It seems unnecessary that a patient who has passed only a single uric acid stone should be put to the inconvenience of trying to keep the urine alkaline for the rest of his life Alkalinization of the urine is best reserved for chronic formers of uric acid stone, for those in whom stones form with great rapidity or for patients who have associated progressive renal damage and obstruction from uric acid stones and sludge The desirability of alkalinization of the urine during initial administration of probenecid has also been suggested

Since alkalinization of acid urine in a patient who forms uric acid stones is advisable, it probably means the patient must undertake a twenty-four hour program, which will probably include the need for oral medication during the usual sleeping hours. Sodium citrate is a satisfactory alkalinizing agent that can be administered in 2 Gm doses every six hours. Sodium bicarbonate may be a more convenient drug and should also be given every six hours in 2 Gm doses. If sodium is contraindicated because of

hypertension or congestive heart failure, potassium citrate can be given if the blood urea nitrogen level is normal Wyngaarden (382) suggested that Diamox[R] be given at bedtime to keep the urine alkaline at night.

The pH of the urine should be determined every morning and evening, and this can be done by the patient, who is taught to use nitrazine paper The urine is alkaline at a pH of 7 or above As pointed out by Peters and Van Slyke (255), the solubility of uric acid at a pH of 5 is only 8 mg. of uric acid per 100 ml, whereas at a pH of 7 it is 158 mg. of uric acid per 100 ml Sodium bicarbonate and sodium citrate allow alkaline urates to remain in solution until excreted

DIET

The full effect of the dietary habits of the patient with gout remains unknown The diet of 221 patients with gout observed by us was not unique, only 10 per cent consumed large amounts of purine, 40 per cent ate more than an average amount of meat (especially beef), and the remaining 50 per cent consumed an average or even lower than average amount of meat and fat Some observers (21) believe that addition or deletion of purine-containing foods or fat to the diet does not change the clinical picture of gout, whereas others (139) have expressed the opinion that these foods influence the course of the disease Most of the older writings (89, 257) are emphatic and meticulous in their dietary advice Current advice agrees on avoidance of overindulgence, obesity and diets that may lead to nutritional deficiencies

There is evidence that ingestion of food with high purine content and large amount of animal (muscle) protein may increase the serum uric acid formation 100 per

cent A diet high in fat will result in reduced renal uric acid excretion with uric acid retention (139, 141).

Modern studies with isotopes have demonstrated that purine in the diet is not the sole source of uric acid. The endogenous supply via synthesis from carbohydrates, fats and protein is always present. This *in vivo* synthesis is controlled by an unknown mechanism, but as it affects the serum uric acid level, the dietary source of uric acid precursors, diets restricted in purines, are probably of limited importance and somewhat unrealistic

Strict dietary restrictions are seldom accepted by the patient who has experienced anything less than severe incapacitating gout or its arthritic residuals. Rare is the patient who follows such a diet, but if the required restrictions are too severe and are followed too closely, serious nutritional deficiencies may develop

Despite the knowledge that endogenous precursors are always available for synthesis of serum uric acid and the known reluctance of patients to accept diets, in view of the presence of an enlarged uric acid pool in patients with gout, it seems reasonable for them to avoid an excessive exogenous supply of such material. On this premise, it seems valid to restrict excessive purines, proteins, and fats from the diets of patients with proved gout The more severe the gout, the more stringent the reduction of proteins, purines, and fats, but not to the point of nutritional deficiencies. Production of uric acid is not appreciably affected by normal carbohydrate intake, but a high carbohydrate diet enhances urate excretion. It has been speculated that when renal glucose excretion is high, there may be competition between the glucose and uric acid reabsorption into the tubules, with subsequent increased excretion of urinary uric acid (44). A patient with acute or interval gout should select his foods from

those given in the list of "Foods Allowed" in Stage II For patients whose gout is difficult to control, there is justification for recommending only those "Foods Allowed" listed for Stage I. Since this would probably prove too monotonous for constant use, addition of small servings of meat would eventually be needed by most patients Severe fasting may be followed by a decrease in uric acid excretion and is to be avoided (192)

Some therapists believe that elimination of the foods listed in "Foods Omitted" in Stage II is all that is necessary for dietary control Neither patient nor physician should expect specific subjective or objective changes from a low-purine, low-fat diet, as this merely reduces the exogenous supply of purine precursors

The cell nuclei furnish the chief exogenous supply of uric acid, and the principal aim is dietary exclusion of those foods with plentiful cell nuclei. A low purine intake could be obtained by excluding those "Foods Omitted" in Stage I, and a modified low purine diet would delete those foods included in the list of "Foods Omitted" in Stage II Gutman and Yu (138) expressed the opinion that if the objective is to minimize urate deposits in tissues, a more restrictive low-purine, low-fat, and limited protein (50 to 75 Gm./day) diet is indicated

Some therapists (15, 158) advise complete abstinence from alcohol in the treatment of gout However, there is little conclusive proof that alcohol is a precipitating agent in acute attacks of gout. For patients desirous of its use, the intake of alcohol is best controlled by temperance rather than abstinence, and should be limited to distilled whiskies All patients should avoid fermented alcoholic beverages, such as wine, vermouth, beer, ale, and champagne (202) There is no need to exclude tea, coffee, and chocolate from the diet, as excretion of uric

acid after their imbibition is proportional to the quantity of caffeine ingested (229), and these beverages actually contain *methylxanthines, which are metabolized to* methyl urates and do not form gouty tophi (358, 369). Urinary output should be maintained at a minimum of two liters daily

Some patients with gout will maintain that certain foods or beverages will precipitate acute attacks. They should, of course, avoid such foods or beverages

These dietary considerations should apply to every patient with gout, regardless of the stage of the disease. We have not noticed any particular advantage of a liquid, low-purine diet at the time of an acute attack, but permit our patients to select the foods they wish from their regular low-purine, low-fat diet. Again, this depends upon what the patient is inclined to eat at this particular time. Medications that cause nausea will, of course, reduce the food intake

Obesity is a problem of many patients with gout Reduction of weight is frequently necessary, but it should be done slowly with a regulated low-purine, low-fat diet Fasting will cause a rise in the serum uric acid level and sometimes increasingly frequent acute attacks of gout (155, 192) Such patients become discouraged with losing weigh and the general condition remains the same. Daily administration of colchicine may prevent acute attacks from occurring while the patient is losing weight.

In patients with hyperuricemia alone without gouty arthritis or uric acid nephrolithiasis, severe dietary restrictions are not necessary. Such patients probably should avoid fermented beverages, overindulgence in any food (especially fat) and glandular meat edibles (See Foods Omitted, stage II)

Although a specific food can seldom be incriminated

as the precipitating factor of an acute attack of gout, it is of interest that in South Dakota the frequency of gout among pheasant hunters has given rise to the term, "pheasant hunters' toe," which is attributed to the trauma of hunting, imbibition of spirits and ingestion of pheasant meat, which has a high purine content (75-100 mg of purine in 100 Gm.) (341)

APPROXIMATE COMPOSITION

	Stage I	*Stage II*
Calories	2308	2245
Protein	116	115
Fat	61	59
Carbohydrate	350	338
Calcium	2 49	2 46
Iron	13 82	14 46
Vitamin A	23075	23570
Thiamin	1 63	1 53
Riboflavin	3 21	3 27
Niacin	21 15	14 91
Ascorbic Acid	285	285

FOODS ALLOWED (STAGE I)

Beverages Coffee, tea, decaffeinated coffee, non fat milk, buttermilk, cocoa (made with non-fat milk), and carbonated beverages

Bread Enriched white bread, plain crackers, and corn-bread

Cereal Refined enriched cereals only, such as cream of wheat, farina, cornmeal, grits, cornflakes, rice kris-pies, and puffed rice

Cheese Cottage and cheddar cheese

Desserts Gelatin desserts, ices or sherbets, rennet desserts, custard, cornstarch, tapioca pudding (made with non-fat milk), angel food or sponge cake, plain cookies and fruit whips

* This diet sheet was compiled, with the assistance of Miss Sara J ...mley, from material contained in the Dietary Manual of the Ochsner ...ndation Hospital

Fat	Butter, enriched margarine, cream, cream cheese, vegetable oil and shortening in amounts allowed Limit to three (3) teaspoons of butter or its equivalent daily.
Fruit	Any fresh, frozen, or canned fruit or fruit juice as desired
Meat.	None
Eggs	Any way except fried
Other Starches.	White and sweet potato, marcaroni, noodles, spaghetti, rice and grits
Soup	Milk soups made with vegetables allowed
Vegetables.	All vegetables except those listed under "Foods Omitted."
Miscellaneous	Salt, sugar, jellies, jams, preserves, honey, hard sugar candy, herbs and spices in moderation, and peanut butter.

FOODS OMITTED

Beverages	Whole milk
Bread	Whole grain breads
Cereals	Whole grain cereals
Cheese	None
Fat	Omit fats in excess of amount specified under "Foods Allowed"
Fruits	None
Meat	All
Eggs	Fried eggs
Soup	Soups made with meat extractives and meat stock
Vegetables	Asparagus, cauliflower, mushrooms, peas, spinach, lima beans, and all dried vegetables
Miscellaneous	Cream sauces and gravies Avoid condiments and spices only if they tend to cause digestive difficulty
Desserts	Rich pies and pastries, ice cream, and any dessert made with whole milk
Other Starches	None

SAMPLE MENU (STAGE I)

Breakfast	*Dinner*	*Supper*
8 oz. Orange Juice	4 tablespoons Peanut Butter	¾ cup Cottage Cheese
¾ cup Rice Krispies	⅔ cup Broccoli	1 small Baked Potato
1 Scrambled Egg	⅔ cup Carrots	½ cup Green Beans
1 Slice Enriched White Toast	Fresh Fruit Salad (no dressing)	Sliced Tomato Salad (no dressing)
1 teaspoon Butter	1 slice Bread	½ cup Gelatin
1 tablespoon Jelly	1 teaspoon Butter	1 slice White Bread
Coffee	1 piece Angel Food Cake	1 teaspoon butter
1 cup Non-Fat Milk	1 cup Non-Fat Milk	1 cup Non-Fat Milk
Sugar		
10 A M	*3 P M*	*8 P M*
1 cup Tomato Juice	1 cup Pineapple Juice	1 cup Non-Fat Milk
		Crackers

FOODS ALLOWED (STAGE II)

Beverages Coffee, tea, decaffeinated coffee, non-fat milk buttermilk, cocoa (made with non-fat milk), and carbonated beverages

Bread Enriched white bread, plain crackers, and corn-bread

Cereal Refined enriched cereals only, such as cream of wheat, farina, cornmeal, grits, cornflakes rice krispies, and puffed rice

Cheese Cottage and cheddar cheese

Desserts Gelatin desserts, ices or sherbets, rennet desserts and tapioca pudding (made with non-fat milk), custard, cornstarch, plain cookies and fruit whips

Fat Butter, enriched margarine, cream, cream cheese, vegetable oil and shortening in amounts allowed Limit to three (3) teaspoons of butter or its equivalent daily

Fruit Any fresh, frozen, or canned fruit or fruit juice as desired.

Meat Use only one two-ounce serving daily, except those meats listed under "Foods Omitted"

Eggs Any way except fried

Other Starches White and sweet potatoes, macaroni, noodles, and spaghetti, rice and grits

Soup	Milk soup made with vegetables allowed
Vegetables	All except those listed under "Foods Omitted"
Miscellaneous	Salt, sugar, jellies, jams, preserves, honey, hard sugar candy, herbs and spices in moderation

FOODS OMITTED

Beverages	Whole milk
Bread	Whole grain breads
Cereal	Whole grain cereals
Cheese	None
Fat	Omit fats in excess of amount specified under "Foods Allowed."
Fruits	None
Meat	Sweetbreads, anchovies, sardines, liver, kidney and brains
Soups	Soups made with meat extractives and meat stock
Vegetables	Lima beans, asparagus, cauliflower, mushrooms, peas, spinach, and all dried vegetables (Small amounts may be used).
Miscellaneous	Cream sauces and gravies
Desserts	Rich pies and pastries, ice cream, and any dessert made with whole milk
Other Starches	None *Sugar as desired in amounts compatible with the daily caloric needs*

SALICYLATE THERAPY

The analgesic properties of salicylates in rheumatic diseases can be utilized to advantage in the management of gouty arthritis One of the oldest known actions of salicylates is to increase urinary excretion of uric acid In 1886, Paton (252) speculated that production of uric acid is decreased after administration of salicylates In 1895 Fawcett (99) noted that uric acid excretion is increased by use of salicylates and speculated that possibly the uric acid stored in the body is of such magnitude that it may take a long time to get rid of it. In 1915 Fine

and Chace (103) noted that salicylates reduced the uric acid concentration of the blood Talbott (324) pointed out the likelihood that this is accomplished by decreasing renal tubular reabsorption of uric acid However, unlike probenecid the action of salicylates appears to be that the renal transport mechanisms are overloaded with salicylate, so that less uric acid is transferred back into the blood stream. This uricosuric effect is accompanied by a modest decrease in serum uric acid In order to obtain this effect, about 4 Gm of salicylates a day or more should be administered (179) One to 2 Gm can actually induce retention of uric acid and the urinary uric acid output is reduced (259) It has been postulated that small doses of salicylates may inhibit tubular excretion or enhance tubular reabsortion of urates, but larger amounts block the tubular reabsorption system of urates

It is also noteworthy that the recommended daily dosage of 5 to 6 Gm of salicylates on three successive days of each week produce no net weekly loss of uric acid (22) The reason for this is that on the days salicylates are not taken uric acid is retained and the serum uric acid level rises Bauer and Klemperer (22) pointed out that with continuous administration of salicylates tolerance develops and serum uric acid levels become stabilized after a few months

According to Kersley and coauthors (172) salicylates are superior to cincophen and carinamide and equal to probenecid in the production of increased uricosuria with concomitant fall in plasma uric acid Marson (224) also supported use of salicylates as a uricosuric agent in gout, preferring them to probenecid He has maintained his patients on unusually large oral doses of salicylates for long periods of time with impressive reduction of urate tophi in some He suggested continuous use of 90 or

more grains of salicylates daily, and stressed the need of its uninterrupted administration.

In gouty patients with elevated blood urea nitrogen levels and severe gouty renal damage, large doses of salicylates may be more effective than probenecid in reducing the serum uric acid level (70, 386). Further evidence of the efficacy of salicylate administration is found in the report of Benedict and associates (26), who showed that in one patient with gout salicylates reduced the miscible pool of uric acid from 31 to 2 Gm. The patients with gout whom Marson (222) treated continuously with salicylates experienced reduction in the incidence of acute attacks. If the patient is sensitive to probenecid, salicylates may be substituted (17).

Some physicians believe that the effects of salicylates and ACTH are extremely similar. The evidence of this type of action is somewhat contradictory and tenuous; the striking similarities lie in the fact that both agents produce uricosuria and deplete the ascorbic acid of the adrenal glands of suitable hypophysectomized rats. Indeed, this latter action is so characteristic of ACTH that it is employed as the standard method for assay of ACTH preparations. However, it has also been known since the pre-insulin era that in many instances salicylates in large doses can reduce the glycosuria of patients with diabetes mellitus. This characteristic has been confirmed and extended in partially pancreatectomized rats. This effect is actually diametrically opposed to that produced by ACTH in similar situations Possibly, salicylates act as inhibitors of insulinase and the ACTH-like effects sometimes seen might also be due to such effects plus the ACTH releasing effect of the increased circulating insulin. Oral and intraperitoneal administration of sodium salicylate to intact

guinea pigs resulted in a great increase in the plasma levels of 17-hydroxycorticosteroids (127)

Salicylates should be given orally There is no advantage in parenteral administration for gout or other arthritic conditions The two most popular preparations are sodium salicylate and acetylsalicylic acid Nausea and vomiting frequently result from administration of large doses of salicylates. This can sometimes be prevented by the simultaneous administration of an equal amount of sodium bicarbonate, which provides protection against release of salicylic acid Gastritis also is common if large amounts of salicylates are used, especially if other medications causing gastric irritation are administered Acute gastric ulcer with bleeding can be the end result of such gastritis. Enteric-coated salicylates can be helpful but are not always dependable, for there is significant variability in the dissolution of the outer coating of the tablets of the various manufacturers Salicylates may cause a painless gastric hemorrhage, which is not due to a demonstrable peptic ulcer but is believed by some (170) to be due to gastric allergy to salicylates

Fortunately, most toxic reactions to salicylates are mild. Allergic reactions do occur but are usually easily detected Salicylates should be given with caution to asthmatic patients, for many of the sensitivity reactions resulting from use of acetylsalicylic acid occur in asthmatics

Salicylate poisoning is prone to occur in patients with renal impairment, so that the presence of nephritis warrants added consideration when large doses of salicylates are prescribed for long periods Doses of 2 to 3 Gm or more of aspirin sometimes may cause albuminuria and appearance of a few white blood cells, casts and an occasional red blood cell in the urine (117) Salicylism may be manifested by tinnitus, headache, dizziness, increasing

eafness, sweating, thirst, nausea, vomiting and mental nfusion Disturbances in the respiratory and cardioscular systems are associated with more serious toxic actions.

PROBENECID

Probenecid (Benemid® [para-di-n-propyl sulfamylnzoic acid]) was introduced for treatment of gout durg the last decade It is one of a family of benzoic acid rivatives, which also includes carinamide, developed to duce renal excretion of penicillin. Its structural formula shown in Figure 56.

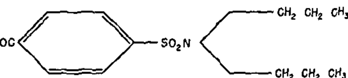


Fig 56: Structural formula of probenecid

Probenecid increases urinary uric acid concentration e site of action is believed to be in or adjacent to the al tubules. It appears to act by inhibiting tubular bsorption of uric acid, though its exact mode of action not known (296). It increases the uric acid in the dder from 50 to 200 per cent; this suggests a decrease tubular reabsorption of from 5 to 20 per cent. This urs within minutes and lasts several hours. Some intigators (335) believe that the renal tubules actively rete uric acid and that probenecid could increase this ivity.

The increase in urinary uric acid is of sufficient magnie to lower the serum uric acid content which in turn ses a "negative balance" and tissue uric acid is deased. There is no apparent refractoriness with contin use of probenecid.

Gutman and Yu (136) noted that the intensity and duration of the uricosuric effect of probenecid varies in different patients receiving the same dosage. The initial uricosuric action of probenecid may be greater during the first few weeks or months than later, despite use of the same dosage and diet. Prolonged use usually results in leveling off of the reduced uricosuric effect. Gutman and Yu believed that the uricosuric effect depends on the mobilizable deposits of urates, and once these are depleted, a controlled level of increased uric acid excretion results. It seems simpler to consider the lower excretion simply in terms of the lower serum uric acid level with a constant action on the renal tubule producing a lower uricosuric effect.

It is generally agreed that its administration may precipitate an acute attack of gout. This occurs most frequently during the initial months of its use, but it has been known to precipitate acute bouts of gout during the first six months of use of the drug. The mechanism of this phenomenon is not known.

Probenecid has no analgesic properties and is of no value in treating acute gout. It does not alter uric acid metabolism but does reduce the metabolic pool of uric acid.

Probenecid is rapidly absorbed from the gastrointestinal tract. Daily doses of more than 2 Gm may cause nausea, vomiting, anorexia, dyspepsia and constipation but such gastrointestinal disturbances are mild and transient with smaller doses. We saw one patient who became confused, dizzy and extremely weak after taking the drug for several days. The symptoms completely subsided when use of the drug was discontinued.

Probenecid seems to have little, if any, harmful effects

on the hemopoietic centers. However, anemia was reported in one patient after receiving probenecid (42).

Sensitization to probenecid occurs in 1 to 2 per cent of patients. Development of dermatitis after administration of probenecid has been reported A severe reaction characterized by pruritus, swelling of the face and scalp, giant urticaria, profuse sweating, weakness, pallor, tachycardia, fall in blood pressure and fever for twenty-four hours was reported; successful desensitization to probenecid was accomplished by daily oral administration of minute doses of the drug for three months (10). Hypersensitivity to probenecid resulting in fatal extensive necrosis of the liver has been reported (268).

One of the serious complications of probenecid therapy is precipitation of uric acid crystals in the kidney or excretory passages (42) This can usually be prevented by sufficient intake of fluid to produce a minimum daily urinary output of 2000 cc. or, if necessary, by alkalinization of the urine

Probenecid apparently has no detrimental effect on renal function as measured by creatinine, mannitol and para-aminohippurate clearances. Phenolsulfonphthalein excretion is inhibited during use of probenecid, but this is corrected when use of the drug is discontinued The few patients who were taking probenecid on whom necropsy was performed, referred to in the literature, did not show renal damage attributable to the drug Gutman and Yu (136) reported development of renal colic in only two of their sixty-two patients who were studied carefully after administration of probenecid.

The beneficial effects after use of probenecid are significant but sometimes vary. Some of our patients reported alleviation of some of the chronic discomfort and stiffness Acute gouty arthritis recurs less frequently or

disappears with continuation of therapy. Diminution of the attacks of gouty arthritis and possibly prevention of urate tophi are the greatest benefits to the patient from prolonged probenecid therapy.

Tophi can disappear or be reduced in size, and permanent articular damage may be prevented or damage may be partially repaired. Further years of observation of patients receiving probenecid therapy are required before it can be said with certainty that destructive articular changes are prevented or that eventual renal damage does not occur.

The very nature of the action of probenecid in gout makes continued administration imperative. Discontinuance of use of the drug for as little as twenty-four to forty-eight hours results in decrease in the urinary uric acid excretion and a beginning increase in the serum uric acid. Many of the good effects of prolonged therapy also disappear although there is some evidence that this may be regained after a shorter term of re-initiation of therapy than that occurring initially.

Using different uricosuric agents might be expected to produce additive effects and use of probenecid and salicylates together would at least be thought to be additive if not synergistic. However, exactly the opposite is true and when these two agents are given simultaneously, the uricosuric effect of either alone is completely lost (251).

Other Uricosuric Agents. Diodrast (321) increases urate clearance, but it must be given intravenously and its action lasts only a few hours. The anticoagulants, ethyl biscoumacetate (242, 306) and bishydroxycoumarin (90), have a significant uricosuric action but the anticoagulant properties preclude its use for the treatment of gout. Their action is compared to dehydroacetic acid, which probably inhibits tubular transport of uric acid. In lim-

ited studies the anticoagulant, heparin, was reported as being helpful in relieving acute gouty arthritis (160).

Zoxazolamine (2-amino-5-chlorobenzoxazole), a drug used initially for relieving muscle spasms, has been found to have a potent uricosuric action (266). This agent is a weak base and has a chemical structure that differs from other known uricosuric drugs. In limited observations small doses (15 to 50 mg.) given to gouty subjects resulted in a threefold to fivefold increase in urinary urate excretion and fall in serum urate. Uricosuria from a single dose lasted about six hours (60). Extensive clinical trials will be essential to evaluate this drug's worth for the gouty patient.

COLCHICINE

One of the earliest known medical agents still in use is colchicine, which is an active alkaloid found in the corm and seeds of colchicum autumnale. This alkaloid is still the cornerstone of therapy for acute gout. The accepted structural formula popularized by von Windaus (364) in 1924 has been replaced by the one suggested by DeWar (87), which is thought to be the probable structure of colchicine

Colchicum autumnale is better known as the meadow saffron and received its name because it grew in Colchis in Asia Minor It blooms in the fall in the wet meadows of southern and central Europe. It was probably initially used in a crude form in criminal poisoning, but it was first recommended for articular pain by Alexander of Tralles in the sixth century A. D. According to Hartung (143), in 1763, Baron Anton Von Storch introduced it for the treatment of gout The alkaloid, colchicine, was not isolated until 1820 (143). Hartung (143) compiled an excellent review of the history of colchicine and its role in medicine.

Despite its long, honored history as a therapeutic agent for gout, its pharmacology in this regard still remains a mystery. Goodman and Gilman (128) considered use of colchicine in gout as "purely empirical" and the mechanism of the dramatic relief afforded by it in acute attacks of gouty arthritis as still enigmatic. It cannot be classified as an analgesic and the relief for gouty pain is specific and does not occur in other types of arthritis.

Little is known about the fate and metabolism of colchicine in man. Brues (52) pointed out that the major route of excretion of colchicine is through the intestines even after intravenous administration. Indeed, the route to the intestine is apparently via excretion in the bile. It is interesting that the biologic half life of colchicine is approximately sixteen hours, which is greater than the duration of the acute mitotic arrest.

The relationship of hyperuricemia and gout remains unexplained. The hyperuricemia is not affected in any known manner by colchicine. This alkaloid is not a uricosuric agent, nor has it been demonstrated that it alters the intermediary metabolism of purines. Of interest are the observations of Laster and Blair (190), who detected in some human and other animal tissue an enzyme, uric acid riboside phosphorylase, that catalyzes release of uric acid from riboside of uric acid. Colchicine appeared to inhibit completely uric acid riboside phosphorylase. Recent studies with isotopically labeled uric acid showed change in the size of the miscible uric acid pool in only one patient after treatment with colchicine. However, Bishop and associates (36) and Talbott and coworkers (329) noted that administration of colchicine to several patients was associated with decrease in the uric acid turnover rate. They believed that administration of colchicine led to a decrease in the rate of synthesis of uric

acid with or without associated decrease in disposal rate such that the size of the miscible pool remained constant, although in one patient it had decreased. Benedict and associates (26) did not find that colchicine had a demonstrable effect on the miscible uric acid pool of the patients they studied.

An attractive explanation for the reduced entrance of the uric acid into the miscible pool during colchicine therapy is that the mitotic arresting ability of the colchicine, to be discussed later, in effect ties up the uric acid precursors in the nuclei of the arrested mitosis and thereby decreases the availability of uric acid precursor in the miscible pool.

Adlersberg and associates (3) noted that in one patient who was treated with colchicine after an acute attack of gout and whose uric acid partition was studied, the bound uric acid was normal whereas before treatment with colchicine, it was elevated. They believed that colchicine exerts its effect by altering the percentage of uric acid which is bound to protein Bene and Kersley (24), who employed modifications of previously reported technics for determination of ultrafiltrable plasma uric acid, found such determinations of no value. We employed technics similar to those of Adlersberg and have been unable to obtain interpretable results.

Moderate to severe sodium and chloride retention in both control and gouty subjects has been reported after therapeutic doses of colchicine, and the chloride retention was in proportion to the diminished urine volume (195).

The characteristic pharmacologic property of colchicine and its relatives is its effect upon cell division, which is not confined to animals but is also seen in plants In plants this effect can sometimes be substantial and long-

lasting, producing polypoid nuclei and often bizarre plants of microscopic or huge size. Excellent studies in which tissue culture methods were employed in the laboratory of Lits and associates (200) in Belgium showed that adequate amounts of colchicine produce arrest of cell division in the metaphase and that usually after the spending of the arresting stimulus the nuclei complete their cell division with no apparent defect.

One of the sites of greatest mitotic activity other than bone marrow in the normal intact organism is the intestine, and mitotic arrest can most readily be demonstrated in the mucosa of the colon. It is interesting to speculate how much of the characteristic gastrointestinal findings are dependent on this activity. Also it is of interest that oral use of colchicine, like heparin, diminishes the visible lipemic response to alimentary fat (238). Injection of colchicine into an acute gouty joint does not appear to have any favorable effect (196).

The predominant side effects of colchicine are referable to the gastrointestinal tract. These reactions usually do not occur in patients receiving reasonable amounts of colchicine. Usually, patients with gout who have taken toxic doses of the drug (usually 0.6 mg every two hours for twelve to fifteen doses or less) will be troubled with mild abdominal cramps, pain, signs of increased peristalsis, mild to moderate nausea, anorexia, and subsequently, acute diarrhea. Whether the purgative action contributes to the efficacy of colchicine has been debated. It may help relieve the pain by reducing edema through electrolyte loss (348). The diarrhea lasts twenty-four to thirty-six hours after use of the drug is discontinued. Blood in the stool of these patients is usually the result of local irritation, low intestinal lesions or rectal lesions, such as hemorrhoids. Also, the gastric irritation may be

so severe that it precipitates bleeding from acute gastritis or it may sufficiently activate an old gastric ulcer to cause bleeding Some patients report that colchicine makes them irritable and restless. Evidence of dehydration often follows the acute diarrhea, but this is probably secondary to the fluid loss from the gastrointestinal tract Goodman and Gilman (128) stated that the patient taking colchicine may have a rapid, weak pulse and feel greatly exhausted Muscular depression and a burning sensation of the throat and skin have also been reported Another rare but serious complication mentioned by Goodman and Gilman is ascending paralysis of the nervous system, which may result in death from respiratory arrest

Wolfson (367) reported sensitivity to colchicine apparently alleviated by administration of corticotropin In 1957 Bauer and Singh (23) wrote that they considered colchicine a safe drug and that except for gastrointestinal symptoms they had observed no untoward effects. They questioned the validity of a fatal case reported as due to hypersensitivity to colchicine (211). They believed that death resulted from depletion of electrolytes and water associated with vomiting and diarrhea. Until 1947, 5 fatal cases of colchicine toxicity had been reported.

The kidney, which is one site of little if any excretion of colchicine, has not shown any evidence of damage However, Goodman and Gilman mentioned that the kidney can be injured, for apparently in animals, large amounts of the drug may cause fat nephrosis, such as that produced by phosphorus and carbon tetrachloride in man.

Occasionally, intravenous administration may be necessary for control of attacks of gout. Gastrointestinal irritation may also occur after intravenous administration

The dosage of colchicine that may cause a gastrointestinal upset is frequently a fixed quantity. Usually the patient's tolerance to the drug can be determined by the number of tablets he takes in a fixed period of time. This varies greatly and is the reason that uniform dosage cannot be prescribed for all patients. The dosage for continuous daily administration of colchicine can usually be adjusted at a tolerated level so that significant recurrences of acute attacks are reduced in frequency. Although extremely rare, the dangers of agranulocytosis and anaplastic anemia are always present. Peripheral neuritis and depilation in blond people after prolonged use of colchicine have been reported (51), as well as weakness of muscles in the legs, which slowly disappeared after use of the drug was discontinued (187).

MODIFICATIONS OF COLCHICINE STRUCTURE

Desacetylmethylcolchicine differs from colchicine in that a methylamine group replaces the acetamide on the second ring. Desacetylthiocolchicine has an amino group replacing the acetamide on the second ring, and a thiomethyl group replacing the methoxy on the third. Wallace (346) believed these two modifications of the colchicine molecule are equally as effective as colchicine in acute gout, whereas colchicoside, which has a glucoside replacing the first methyl group on the first ring, is less effective and colchiceine in which a hydroxy group replaces the methoxy on the third ring of isocolchicine rather than colchicine has no effect on gout.

CINCHOPHEN

Cinchophen (2-phenylquinoline-4-carboxylic acid) resembles salicylates in its antipyretic and analgesic actions. It also has uricosuric action. It was used rather widely

o severe that it precipitates bleeding from acute gastritis r it may sufficiently activate an old gastric ulcer to ause bleeding Some patients report that colchicine nakes them irritable and restless Evidence of dehydraion often follows the acute diarrhea, but this is probably econdary to the fluid loss from the gastrointestinal tract. ;oodman and Gilman (128) stated that the patient takng colchicine may have a rapid, weak pulse and feel reatly exhausted Muscular depression and a burning ensation of the throat and skin have also been reported nother rare but serious complication mentioned by ;oodman and Gilman is ascending paralysis of the nervus system, which may result in death from respiratory rrest.

Wolfson (367) reported sensitivity to colchicine aparently alleviated by administration of corticotropin In 957 Bauer and Singh (23) wrote that they considered olchicine a safe drug and that except for gastrointestinal mptoms they had observed no untoward effects They uestioned the validity of a fatal case reported as due hypersensitivity to colchicine (211). They believed at death resulted from depletion of electrolytes and ater associated with vomiting and diarrhea. Until 1947, fatal cases of colchicine toxicity had been reported

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patients with gout Others (174, 183, 313) failed to demonstrate sufficient uricosuria to account for the fall in plasma urate in patients whose gout was treated with phenylbutazone This discrepancy possibly has been explained by Yu and coauthors (388), who pointed out that the uricosuria depends primarily on the presence of unbound phenylbutazone in the plasma Significant quantities of unbound phenylbutazone occur only when the drug is given in larger amounts than ordinarily used, and these investigators implied that the freely filterable (unbound to protein) phenylbutazone in the blood must be almost completely reabsorbed in the tubules, and this in some manner interferes with tubular reabsorption of urate Unbound phenylbutazone, if found in urine, is only in small amounts Only when the plasma phenylbutazone level exceeds 10 mg per cent does significant uricosuria occur

Administration of phenylbutazone has a pronounced effect on water and electrolyte balance Retention of sodium and chloride and increase in weight occur with decrease in urinary output and fluid retention The fluid retention may also cause dilution of the total plasma uric acid. Wyngaarden (379) showed that this drug causes expansion of extracellular fluid volume Apparently, glomerular filtration is not affected by phenylbutazone but tubular reabsorption of water and salt is increased Diuresis with reduction in weight usually occurs within twenty-four hours after use of phenylbutazone is stopped Sodium retention can be reduced by restriction of salt intake Potassium excretion is unaffected

Yu and associates (388) noted no significant inhibition of the uricosuric effect of either phenylbutazone or probenecid when administered simultaneously

Phenylbutazone may also cause uricosuric action in

for treatment of gout until two decades ago Besides the same potentialities for poisoning as salicylates, cinchophen has a hepatotoxic effect, which was the reported cause for the significant number of fatalities until 1936. Toxicity occurred regardless of the dosage or response to previous medication, and sometimes continued after use of the drug was discontinued The hepatic injury resulting from cinchophen has been reported as toxic cirrhosis, which may proceed to fulminating yellow atrophy In 1936, Palmer and Woodall (249) concluded that there was no safe method of administration of cinchophen This drug is mentioned only to point out that it differs from colchicine, with which it has been confused in the past, and to advise against its use in gouty arthritis.

PHENYLBUTAZONE

Phenylbutazone (Butazolidin®, 3,5-dioxo-1, 2-diphenyl-4-n-butyl pyrazolidine) was introduced into clinical therapeutics in 1951 as an antirheumatic antiphlogistic, and analgesic agent. Its administration may relieve the acute inflammatory symptoms of gout in twenty-four to forty-eight hours. Orally administered phenylbutazone is absorbed quickly and completely from the gastrointestinal tract. The drug is metabolized by poorly understood routes at the daily rate of 10 to 30 per cent (58, 78, 148)

Conflicting opinions have resulted from studies of the effect of phenylbutazone on the metabolism of uric acid in patients with gout and in normal subjects There is general agreement that use of the drug will result in reduction of the elevated plasma urate level, but it has not been completely accepted that this is due to increased excretion of uric acid (226). Mason (226) and Bishop and Beecher (35) noted a consistent uricosuric effect sufficient to account for the reduction of plasma urate in

patients with gout Others (174, 183, 313) failed to demonstrate sufficient uricosuria to account for the fall in plasma urate in patients whose gout was treated with phenylbutazone. This discrepancy possibly has been explained by Yu and coauthors (388), who pointed out that the uricosuria depends primarily on the presence of unbound phenylbutazone in the plasma Significant quantities of unbound phenylbutazone occur only when the drug is given in larger amounts than ordinarily used, and these investigators implied that the freely filterable (unbound to protein) phenylbutazone in the blood must be almost completely reabsorbed in the tubules, and this in some manner interferes with tubular reabsorption of urate. Unbound phenylbutazone, if found in urine, is only in small amounts Only when the plasma phenylbutazone level exceeds 10 mg per cent does significant uricosuria occur

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Phenylbutazone may also cause uricosuric action in

patients in whom prolonged administration of cortisone has caused hyperuremia and gout (18).

Apparently about one-third of the administered phenylbutazone ends in the plasma. This is bound to protein Once the plasma protein is saturated, the remainder is metabolized and excreted in the urine. In clinical administration the saturation level appears to be attained when 400 to 600 mg of the drug is taken daily (58). This negates the need for larger doses, which is associated with a toxicity incidence of 75 per cent

Phenylbutazone has significant toxic effects. These can be related to the hemopoietic center, the gastrointestinal system, the skin, and the electrolyte and water balance Unfortunately, complications, such as optic atrophy and toxic psychosis, have also occurred (96). Other reactions that have been reported are hematuria, swelling of the salivary gland, and general hypersensitivity (183, 313). Several investigators (185, 253) noticed that females are more susceptible to side reaction than males (females 45 per cent, males 28 5 per cent).

Toxic reactions occurred in 30 to 35 per cent of patients taking phenylbutazone, and in 10 to 12 per cent of these, use of the drug had to be discontinued (97, 102). A number of deaths has been attributed to complications from the drug (97, 102). Kuzell and coauthors (185) and Maurer (228) noted a substantially lower incidence and severity of side reactions from phenylbutazone in patients treated for gout than for rheumatoid arthritis or osteoarthritis.

The tendency of the drug to cause sodium and water retention results in peripheral or pulmonary edema in about 13 per cent of patients treated. This is risky in patients with any degree of congestive heart failure A

low salt diet usually controls this complication Mercurial diuretics are not always effective

Gastrointestinal disturbances occur in about 13 per cent of patients taking phenylbutazone Nausea, epigastric pain and stomatitis are the commonest complaints Because precipitation or activation of a peptic ulcer can follow use of phenylbutazone, a history of peptic ulcer is a contraindication to routine administration of the drug Transient hepatitis has been reported (67), however, hepatic function seldom becomes altered, or if it does, it reverts to normal shortly

Serious complications affecting the bone marrow and blood have occurred in about 2 to 4 per cent of patients taking phenylbutazone Hemodilution due to edema may cause what appears to be secondary anemia Aplastic anemia, agranulocytosis, leukopenia and thrombocytopenia have been reported in conjunction with use of phenylbutazone (33, 312, 317)

Cutaneous reactions occur in 5 per cent of patients as simple maculopapular eruptions A purpuric rash is thought to be a reflection of a more serious condition Discontinuance of the drug is usually followed by disappearance of the rash

Phenylbutazone often is extremely effective in acute attacks of gout Complete subsidence within seventy-two hours has been reported in 85 to 95 per cent of patients Because it does not cause the gastrointestinal upsets frequently associated with colchicine, it is the drug of choice of many patients with gout If the drug can be safely used for three to five days, it is a helpful therapeutic agent.

Prolonged used of phenylbutazone invites toxic reactions Although some observers consider it safe and valuable in controlling chronic gouty arthritis, we believe

that its use should be considered only in selected ca
in which the risk is appreciated and justified

Related drugs in this family may afford more effe
tive action. One of these phenylbutazone analogu
[(4-phenylthioethyl)-1,2-Diphenyl 3,5-pyrazolidinedion
(G-25671), proved to be a potent uricosuric agent in th
teen patients, but these initial studies have not be
sufficient to determine their safety or clinical usefulne
(391). Another such agent, G-28315* (sulfoxy phenylp
razolidine), which is a sulfoxide metabolite of G-2567
has had an equally effective uricosuric action on gout (17
242). These two agents appear to be three and six tim
as potent as probenecid, respectively. The anti-inflamm
tory effect is less than that of phenylbutazone. Thes
limited reports include a few toxic reactions, and
further trials prove they are equally as safe as probeneci
another valuable uricosuric agent will be available. A
with probenecid, salicylates seem to counter the uric
suric effect if administered simultaneously. The thre
hour half life of G-28315 necessitates administration o
100 mg four or more times daily. The effect of the intens
uricosuria on the kidneys will bear watching.

HORMONES

Administration of adrenocorticotrophic hormone (ACTH) (219) or cortisone will frequently alleviate acute gouty arthritis These drugs have many effects on the intact organism, such as their influence on metabolism, the electrolytes and water (85) which apparently have no direct connection with alleviation of the acute gouty symptoms. It is believed that their antiphlogistic and antipyretic properties are responsible for the favorable action.

* Anturan ®

Wolfson and associates (374) theorized that the patient with gout is unable to restore as quickly as is needed a "normal adrenocortical status" when a state of lack of adrenal glycocorticoids ("corticoid-lack") is induced by withdrawal of exogenous ACTH, owing to decrease in the rate of secretion of endogenous ACTH or increase in the rate at which the peripheral tissues are utilizing adrenal glycocorticoids. The normal person is capable of restoring normal adrenocortical status by prompt secretion of increased amounts of ACTH when there is corticoid-lack. Wolfson and associates' theory is that patients with gout require relatively large amounts of exogenous ACTH to stimulate the adrenal cortex. If the theory is correct, the effectiveness of oral or parenteral administration of cortisone, hydrocortisone and their analogues could be explained on a replacement basis. There is much to be desired in such an explanation.

Intra-articular injection of hydrocortisone into an acutely gouty joint may result in relief of pain and swelling in a few hours. The mode of action is unknown. The injected steroid quickly disappears from the suspension in the synovial fluid and appears to be absorbed by synovial and joint fluid cells (158). The injected steroid is metabolized and its metabolite may be the factor responsible for its action.

ACTH and cortisone probably should not be given to a patient with an active peptic ulcer or a generalized bacterial or viral infection. Colchicine should be given in small daily doses (0.5 mg twice a day) during and after use of ACTH or cortisone, as prophylaxis against a rebound attack of acute gouty arthritis due to withdrawal of these agents.

Testosterone has been reported occasionally to have alleviated acute gouty arthritis (159).

Chapter XII

PROGNOSIS

THE clinician usually obtains considerable satisfaction from treating patients who have gout. This probably is a reflection of the favorable therapeutic response of the acute attacks and more recently the beneficial effect of uricosuric agents for chronic gout.

The earlier in life gout appears the greater the likelihood of recurrences of acute gouty arthritis and subsequent chronic gouty arthritis; consequently, the more serious the prognosis From 60 to 70 per cent of patients with gout between the ages of 35 and 50 years have more than a single attack Probably half of these will have some incapacitation from gouty arthritis or its complications in subsequent years.

Talbott (326) maintained that more than 90 per cent of patients with gout lead normal lives and suffer surprisingly little, and not more than 2 or 3 per cent will die prematurely of the disease. Apparently fewer patients with extensive tophaceous gout are seen in medical clinics now than formerly. In certain patients with tophaceous gout uricosuric drugs effect reduction in the size of soft tissue uric acid tophi (Fig. 57) and recalcification of osseous gouty defects (Fig. 58). Yu (385) noted that in 82 patients with tophaceous gout treated with uricosuric drugs (probenecid, salicylates, G25671 and G28715) from six to twelve months no new tophi appeared and in 44 per cent (36 patients) the tophi became considerably smaller or completely disappeared. This could mean

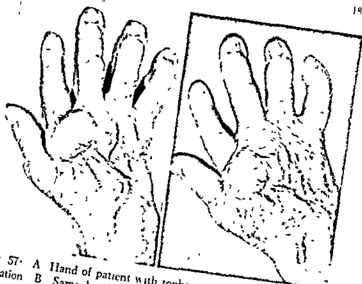


Fig 57· A Hand of patient with tophaceous gout of twenty years' duration B Same hand after 22 months of probenecid therapy, showing significant reduction in size of large tophus overlying dorsal surface of second metacarpophalangeal joint

that with more effective agents the deformities commonly associated with gout could frequently be corrected

Patients with gout in whom related renal impairment develops offer the most critical picture Subsequently pyelonephritis and hypertension may develop, only to add to the gravity of the situation The renal impairment does not necessarily parallel the degree of chronic gouty arthritis, and may develop with little evidence of generalized uratosis. Renal insufficiency can remain stationary for eight or more years, and with the use of more potent uricosuric drugs partial reversal of this process is possible



Fig 58: A. First metatarsophalangeal joint shows destructive cystic gouty changes B Note improvement three years later. Patient had received continuous colchicine and probenecid therapy in the interim

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